UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

In re AVEO Pharmaceuticals, Inc. Securities Litigation	Civ. A. No. 1:13-cv-11157-DJC
	CLASS ACTION
This document relates to: All Actions	Hon. Denise J. Casper
	THIRD CONSOLIDATED AMENDED COMPLAINT FOR VIOLATIONS OF FEDERAL SECURITIES LAWS
	DEMAND FOR JURY TRIAL
	Leave to file granted by Dkt. No. 115

Lead Plaintiffs Robert Levine and William Windham ("Plaintiffs"), individually and on behalf of all other persons similarly situated, by their undersigned attorneys, for their complaint against Defendants, allege the following based upon personal knowledge as to themselves and their own acts, and information and belief as to all other matters, based upon, inter alia, the investigation conducted by and through their attorneys, which included, among other things, review of the Defendants' public documents, conference calls, television appearances and announcements made by Defendants, United States Securities and Exchange Commission ("SEC") filings, wire and press releases published by and regarding AVEO Pharmaceuticals Inc. ("AVEO" or the "Company"), briefing documents and transcripts published by the United States Food and Drug Administration ("FDA"), analysts' reports and advisories about the Company, the March 29, 2016 complaint filed by the SEC against AVEO, and information readily obtainable on the Internet.

NATURE OF THE ACTION

1. This is a federal securities class action on behalf of a class consisting of all persons other than defendants who purchased AVEO common stock between May 16, 2012 and May 1, 2013, both dates inclusive (the "Class Period"), seeking to recover damages caused by Defendants' violations of the federal securities laws and to pursue remedies under the Securities Exchange Act of 1934 (the "Exchange Act").

2. AVEO is a biopharmaceutical company focused on discovering, developing, and commercializing cancer therapies. At all times relevant hereto, AVEO's lead product was tivozanib (trade name Tivopath), an oral inhibitor of the vascular endothelial growth factor receptors ("VEGF inhibitor") that the Company aims to commercialize as a targeted treatment for advanced renal cell carcinoma, the most prevalent form of kidney cancer. During the Class Period, AVEO had no other advanced stage products in its development pipeline, and was valued by the market based primarily on the prospects for tivozanib.

3. Defendant Tuan Ha-Ngoc joined AVEO, then known as GenPath Pharmaceuticals, in 2002 as its President, Chief Executive Officer and Director. At his first meeting of the board of directors, Ha-Ngoc laid out a 10-year plan culminating in the filing of the Company's first new drug application ("NDA") in 2012. Ha-Ngoc frequently discussed the importance of this 10-year plan in his media appearances. For example, he told *BioCentury* that the plan was his "vision" and he "wanted to know if the people were on board or not from the beginning,"[1] Ha-Ngoc understood that his vision depended upon raising money from outside investors: "money buys you time, and

[1] *See* http://www.biocentury.com/promotions/GrowingMidTierBiopharma/genzyme-other-biotech-pioneers-may-go-but-mid-tier-biopharma-is-growing-a1.htm

… time and money are key ingredients for innovation."[2]

4. In 2006, AVEO jump-started its drug development efforts by licensing rights to a proprietary compound called tivozanib from Kirin Brewery Company of Japan. AVEO believed that tivozanib could fight certain cancerous tumors by inhibiting angiogenesis, thus starving the tumor of the blood supply needed to grow.

5. After setbacks in early clinical trials of another drug candidate, ficlatuzumab, AVEO focused the vast majority of its efforts on developing tivozanib. By the time that AVEO went public in March 2010, its prospectus described tivozanib as its "lead drug candidate."

6. In December 2008 and May 2009, AVEO met with the FDA regarding the design of a Phase 3 trial assessing tivozanib as a first-line treatment for renal cell cancer. The study, known as TIVO-1, tested tivozanib against an already approved but outdated drug, sorafenib. TIVO-1 was the only pivotal clinical trial that AVEO conducted to support an NDA for tivozanib.

7. Defendants did not conduct TIVO-1 in the manner discussed and agreed upon with the FDA. Instead, they took three shortcuts which helped speed enrollment, make the study less expensive, and boost results, but compromised its scientific integrity. Specifically, Defendants – in contravention of the agreed design discussed with the FDA – modified TIVO-1 to include three defects:

A. One-way crossover: to reduce dropouts in the control arm, especially in Central and Eastern Europe, AVEO provided a free second-line therapy as an incentive to control arm patients. No second-line therapy was provided to experimental arm patients. While this perk helped discourage patients from dropping out once they

[2] *See* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564307/

learned they were to receive the outdated control arm drug, adding a second therapy in an uneven, unscientific manner necessarily confounded the ability to assess overall survival (or "OS") (the ultimate prolongation of patient lives).

B. Extreme geographic concentration: Instead of enrolling patients on the globally dispersed basis discussed with the FDA, AVEO enrolled the overwhelming majority of study participants in a discrete region, Central and Eastern Europe, where scientific testing was less expensive but the patient population was not comparable to the United States due to regional differences in renal cancer treatment.

C. Biased dose-reductions: Defendants arranged for the dosages to be reduced at materially different rates if a study patient became intolerant to the full protocol-specified dose. Dosage rates of the control drug, sorafenib, were cut by 50% when the dose was reduced (with the option for investigators to further halve the dosage), whereas rates of tivozanib were only reduced by 33% (with no option for further reduction).

8. TIVO-1 enrollment began in or around February 2010 and completed ahead of time in or around August 2010. Accordingly, by May 2012, Defendants had between eighteen months and twenty-four months of trial data for each enrollee. By that time, a serious adverse trend had emerged in the data: patients randomized to the tivozanib arm of TIVO-1 were dying at a faster rate than those in the control arm. Defendants hypothesized that the adverse trend might have been caused by their decision to provide the control arm with a second line of therapy in the one-way crossover incentive, rather than efficacy or safety problems in tivozanib.

9. On May 11, 2012, AVEO had a formal, documented Pre-NDA meeting with the FDA to discuss the Company's anticipated NDA submission. As specified herein, Defendants Ha-Ngoc, Johnston and Slichenmyer each either personally attended the May 11, 2012 Pre-NDA meeting or had actual knowledge of its contents within twenty-four hours thereafter. Thus, each knew the full truth at the time he made the false and misleading statements to investors specified herein.

10. In the Pre-NDA meeting, the FDA: (i) recommended that AVEO conduct a whole new well-controlled pivotal clinical trial in an appropriate patient population; (ii) expressed serious concern about the higher death rate in the tivozanib arm of the TIVO-1 study; (iii) criticized the Company's decision to modify TIVO-1 to include a one-way crossover; (iv) questioned whether AVEO should file an NDA at all in light of the compromised TIVO-1 study; and (v) warned that the defective design of the TIVO-1 study made it difficult to tell whether tivozanib was "toxic."

11. The request for a second pivotal clinical trial was particularly devastating, as it would both require enormous amounts of capital that AVEO did not have and take years to conduct, during which AVEO's better-funded competitors like Pfizer could launch second-generation renal cancer therapies and capture market share.

12. Defendants, recognizing that the FDA's request for a second randomized trial posed an even greater threat to AVEO than these competitive pressures, scrambled to put together a second randomized trial called TIVO-2. Within 30 days of the pre-NDA meeting, Defendants had put together a draft study protocol and secured board approval for an $83 million budget.

13. In or before July 2012, AVEO requested a meeting with the FDA to further discuss the proposed second trial and address the FDA's concerns regarding OS. In the meeting request

AVEO told the FDA that it would proceed with the second clinical trial recommended at the pre-NDA meeting, and included a draft protocol for the FDA's approval.

14. In August 2012, the FDA issued a written response to AVEO's meeting request, in which it raised "significant concerns regarding the trial design described," including the fact that the proposed new trial, like TIVO-1, was not designed to adequately measure OS.

15. Just two days later, in light of the FDA's refusal to greenlight the hastily-assembled trial protocol, AVEO withdrew its meeting request. Defendants were expressly warned by their commercial partner, Astellas, that refusing to meet with the FDA imperiled tivozanib approval. Defendants defied the FDA's advice, and declined to conduct the requested second pivotal clinical trial. Instead, Defendants decided to take a massive regulatory gamble by filing the NDA solely on the basis of the single pivotal TIVO-1 trial the FDA had already criticized.

16. However, Defendants were not honest with investors regarding the enormous risks they were undertaking. While speaking to investors regarding TIVO-1, regulatory communications and their NDA, Defendants consistently omitted crucial unfavorable information, ensuring that investors were misled. Specifically, Defendants concealed:

A. that the FDA had recommended a second randomized trial in a comparable population, that was adequately powered and properly designed to measure the OS effect of tivozanib;

B. that AVEO had severely confounded the results of TIVO-1 by deviating from the trial design discussed with the FDA;

C. that the FDA had expressed serious concerns regarding the adverse trend in overall survival;

D. that the FDA questioned whether AVEO should even file an NDA; and

E. that the FDA had expressly indicated that the adverse trend in overall survival could affect approvability.

17. On August 2, 2012, AVEO admitted for the first time that the FDA had concerns about overall survival statistics, even though the FDA had communicated this information to AVEO by May 11, 2012. In reaction to this partial disclosure, AVEO shares dropped from $13.30 to close at $9.75, a decline of nearly 27%, on very high volume.

18. Although the August 2, 2012 drop was severe, AVEO was able to limit the decline by omitting the most important information that the FDA conveyed to it regarding overall survival. Defendants did not disclose that the agency had recommended a second adequately-powered trial in a comparable population, that the agency questioned whether AVEO should even file an NDA, or that the agency had expressly warned that adverse overall survival trends could affect approvability.

19. In December 2012, the FDA reiterated to AVEO that ***overall survival remained*** "a significant safety concern." Defendants, however, continued to mislead investors with respect to TIVO-1, regulatory communications, and the NDA.

20. The FDA scheduled an advisory committee meeting for consideration of tivozanib to take place on May 2, 2013. An advisory committee is a committee that the FDA convenes under the procedures established by the Federal Advisory Committee Act ("FACA"), 5 U.S.C. App. 2, and regulations promulgated thereunder, to provide the FDA with independent technical advice. Because FACA requires that advisory committee meetings be open to the public and advisory committee briefing documents be disclosed to the public, FDA advisory committees also provide a unique forum for the public to gain insight into FDA concerns about drug applications that would

otherwise remain silent. *See* FACA, http://www.acus.gov/research-projects/federal-advisory-committee-act.

21. On March 8, 2013, just before the truth was revealed, AVEO sent the FDA another meeting request, requesting that the agency grant it permission to conduct the requested second trial on a post-approval basis, rather than pre-approval as pivotal trials are conducted by default and as had been discussed with the FDA in the pre-NDA meeting. The FDA categorically rejected this request.

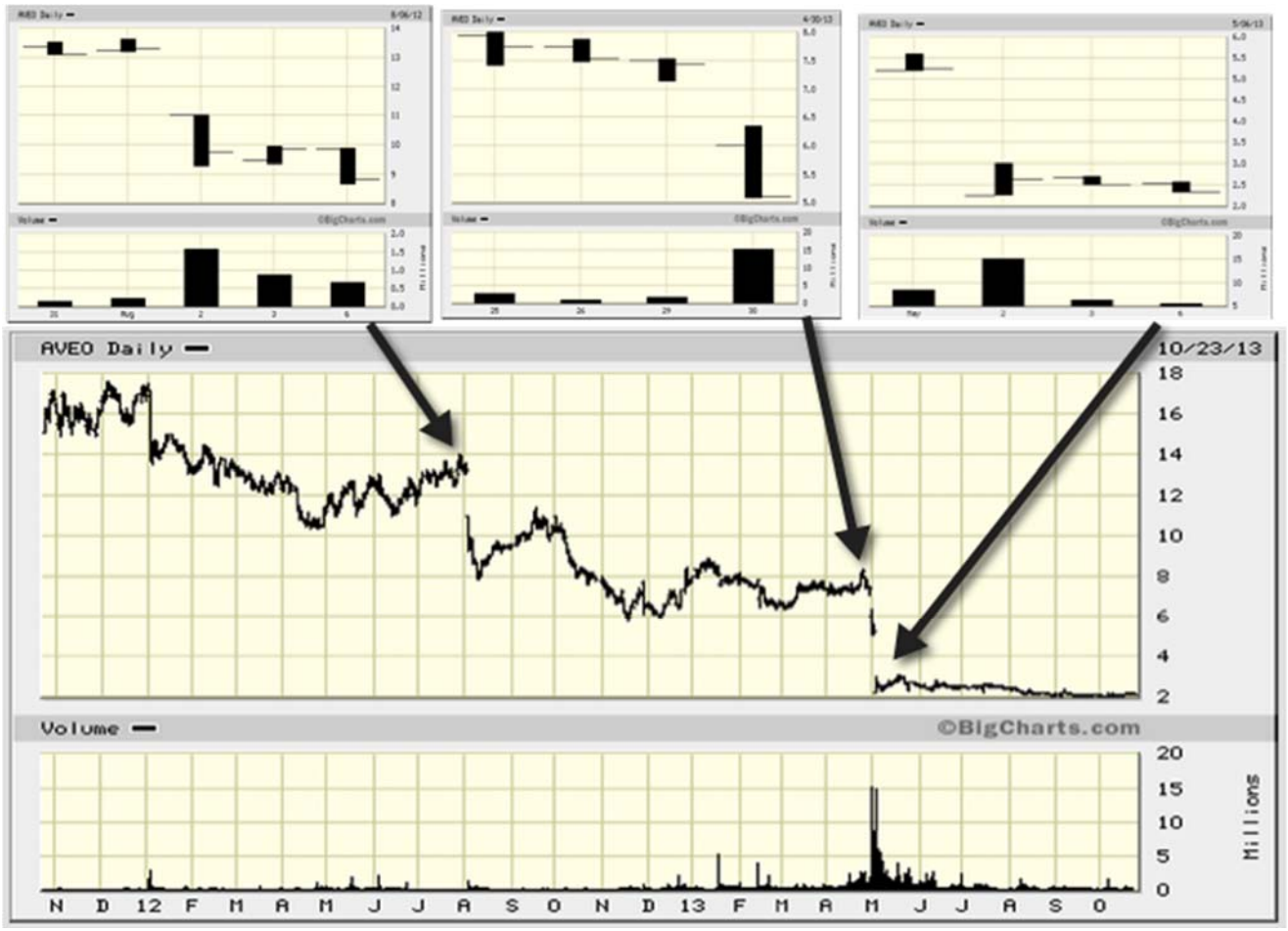
22. On April 30, 2013, the FDA released its Oncologic Drugs Advisory Committee ("ODAC") briefing document (the "Briefing Document") that, among other matters, criticized the design and conduct of AVEO's only pivotal clinical trial, and revealed that the FDA had asked AVEO a year earlier to conduct another clinical trial that was better designed and in a comparable patient population, but the Company had disregarded its advice. Specifically, the Briefing Document explained that "[a] pre-NDA meeting was held in May 2012. Here, the FDA expressed concern about the adverse trend in overall survival in the single Phase 3 trial ('TIVO-1') and recommended that the sponsor [AVEO] conduct a second adequately powered randomized trial in a population comparable to that in the US."

23. In response to the further revelations disclosed in the FDA's Briefing Document, AVEO shares fell $2.33 or 31.31% per share to close at $5.11 on April 30, 2013, on volume of over 15 million shares.

24. On May 2, 2013, the Company and the FDA made presentations to the ODAC panel regarding the new drug application of tivozanib. The FDA noted in its presentation that: (a) tivozanib actually increased potential risk of death by 25% compared to the control drug, sorafenib; (b) TIVO-1 had a flawed trial design as a result of intentional deviations from the design discussed

with the FDA; and (c) due to these design flaws, TIVO-1 provided internally inconsistent trial results, uninterpretable overall survival results, and inconclusive risk-benefit data. The ODAC voted by an overwhelming majority, 13 to 1, not to recommend approval of tivozanib, because, "the application for investigational agent tivozanib did not demonstrate a favorable benefit-to-risk evaluation for the treatment of advanced renal cell carcinoma (RCC) in an adequate and well-controlled trial."

25. When the stock, which was halted during the ODAC panel presentation, began to trade again, it dropped sharply as a result of the further disclosures made during the ODAC presentation. In the afternoon of May 2, 2013, AVEO shares declined $2.61 per share or nearly 50%, to close at $2.65 per share, on volume of over 15 million shares. The chart below demonstrates that each of the three partial disclosures identified herein (August 2, 2012; April 30, 2013; and May 2, 2013) was immediately followed by a substantial, high-volume decline in AVEO's common stock:



26. As a result of Defendants' wrongful acts and omissions, and the precipitous decline in the market value of the Company's securities, Plaintiffs and other Class members have suffered significant damages.

JURISDICTION AND VENUE

27. The claims asserted herein arise under and pursuant to Sections l0(b) and 20(a) of the Exchange Act, 15 U.S.C. §§ 78j(b) and 78t(a), and Rule l0b-5 promulgated thereunder by the SEC, 17 C.F.R § 240.10b-5.

28. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1337, and Section 27 of the Exchange Act, 15 U.S.C. § 78aa.

29. Venue is proper in this District pursuant to Section 27 of the Exchange Act, and 28 U.S.C. § 1391(b). AVEO maintains its principal place of business in this District and many of the acts and practices complained of occurred in substantial part herein.

30. In connection with the acts alleged in this complaint, Defendants, directly or indirectly, used the means and instrumentalities of interstate commerce, including, but not limited to, the mails, interstate telephone communications, and the facilities of the national securities markets.

PARTIES

31. Plaintiff Robert Levine purchased AVEO common stock during the Class Period as set forth in the certification previously filed with this Court and was damaged as the result of Defendants' wrongdoing as alleged in this complaint.

32. Plaintiff William Windham purchased AVEO common stock during the Class Period as set forth in the certification previously filed with this Court and was damaged as the result of Defendants' wrongdoing as alleged in this complaint.

33. Defendant AVEO is a corporation organized under the laws of the state of Delaware, maintaining its principal place of business at 75 Sidney Street, Cambridge, Massachusetts 02139. AVEO's common stock trades on the NASDAQ Global Stock Market ("NASDAQ") under the ticker symbol "AVEO."

34. Defendant Tuan Ha-Ngoc ("Ha-Ngoc") was President, Chief Executive Officer, and Director of AVEO at all times relevant hereto. He was charged by the board of directors with overseeing all corporate goals, including the advancement of the AVEO's development and approval efforts for tivozanib, which was designated by the compensation committee of the board of directors as AVEO's most important corporate goal prior to and during the class period.

Defendant Ha-Ngoc's employment agreement provides that his duties include "the supervision, direction and control over the business and affairs of the corporation and its employees." Defendant Ha-Ngoc has substantial experience with the new drug approval process, and had previously served as an Executive Vice President in charge of legal and regulatory affairs for Genetics Institute, a biotechnology company sold to drug giant Wyeth Pharmaceuticals. Defendant Ha-Ngoc is known to be a micromanager, and at AVEO has routinely involved himself in minute details such as designing Aveo's corporate logo, which Ha-Ngoc did himself using his desktop computer.

35. Defendant David N. Johnston ("Johnston") was AVEO's Chief Financial Officer at all times relevant hereto. He is charged by the board of directors with assisting achievement of the corporate goals and pursuing individual goals including, *inter alia*, maintaining relationships with the financial community and leading the equity financings that AVEO conducts.

36. Defendant William Slichenmyer ("Slichenmyer") was AVEO's Chief Medical Officer at all times relevant hereto. He is charged by the board of directors with assisting achievement of the corporate goals and pursuing individual goals including, *inter alia*, leading the clinical and regulatory efforts to advance the development of tivozanib.

37. The defendants referenced above in ¶¶ 34-36 are referred to herein as the "Individual Defendants."

SUBSTANTIVE ALLEGATIONS

BACKGROUND

The FDA New Drug Approval Process

38. In the United States, pharmaceutical development and marketing is regulated by the FDA, an agency of the U.S. Department of Health and Human Services. The modern

regulatory regime was enacted in 1962, after Thalidomide, a sleeping pill, caused birth defects in thousands of babies. In reaction to this tragedy, Congress passed the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act (the "FDCA") requiring that any company that wanted to market a pharmaceutical product in the United States (in industry parlance, a "sponsor") had to obtain prior approval from the FDA, and that the approval had to be based upon substantial scientific evidence demonstrating that the product was safe and effective for its intended use in humans.

39. The FDCA, as amended, requires the Commissioner of the FDA to refuse any drug application if:

- "he has insufficient information to determine whether such drug is safe for use under such conditions;" or
- "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."

21 U.S.C. § 355(d)(4)-(5).

40. The FDA is only permitted to consider clinical evidence to be "substantial," and thus satisfy the FDCA, if it:

> consist[s] of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d). Well-controlled clinical investigations measure the subject drug against a control group, which is provided either a placebo or another already approved drug for comparison.

41. The sponsor, not the FDA, is responsible for determining the design of clinical trials and the protocols for each trial. If a sponsor wants the FDA to agree that a particular trial or trials are sufficient for approval in the event that endpoints are met, the sponsor may request a Special Protocol Assessment pursuant to 21 U.S.C. § 355(b)(5)(C). Under this provision, the FDA and sponsor meet to discuss the sponsor's proposed protocols, and reduce any agreements to writings that become part of the administrative record. Such agreements may not be changed except by mutual consent or under exceptional medical or scientific circumstances. *Id.* AVEO did not apply for, and did not receive, any Special Protocol Assessments in connection with the TIVO-1 trial of tivozanib.

42. Sponsors are also responsible for enrolling patients in clinical trials. Enrollment can be a lengthy and expensive part of a clinical trial, especially in a larger trial, a trial for a rare disease, or a trial in a field with other competing studies. Regardless of where patients are enrolled, a sponsor must ensure that the trial is conducted according to protocol, and must demonstrate benefit to the patient population for which approval is sought.

43. A sponsor generally conducts clinical trials in three phases. These phases, which are codified in FDA regulations, are as follows:

A. Phase 1. Phase 1 studies "are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."

B. Phase 2. Phase 2 studies are "typically well controlled" studies "conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug."

C. Phase 3. Phase 3 studies are expanded studies "performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects."

21 C.F.R. § 312.21. Those studies which a sponsor uses to support approval in an NDA are known as "pivotal" clinical trials.

44. As AVEO itself acknowledged in its pre-Class Period SEC filings, the FDA encourages sponsors to meet with them for guidance and direction regarding study design. Dr. Richard A. Guarino, a renowned expert on the NDA drug approval process and author of the leading guidebook on the topic, "New Drug Approval Process, Fifth Edition" (CRC Press 2009), explains: [3]

> In addition to meetings before the first human trials begin, the FDA encourages sponsors to meet with the proper division at the FDA at two critical junctures during the drug, biologic and device new product approval process:
>
> (a) *End of Phase 2 meeting:* This meeting will discuss the outcome and significance of the Phase 2 program before the sponsor begins

[3] Dr. Guarino was retained by Plaintiffs to provide background information on the NDA process at the FDA. Dr. Guarino has over 40 years of industry experience. Dr. Guarino has served as Director of Clinical Research at Sandoz Pharmaceuticals, Inc. (now Novartis), Vice President and Medical Director at USV Pharmaceuticals (later called Revlon Healthcare), and Chief Medical and Regulatory Director of Validus Pharmaceutical LLC. For more than thirty years, he has consulted with numerous pharmaceutical companies of all sizes regarding clinical research, FDA regulatory process, and other related topics. He has been an Associate Professor at Farleigh Dickinson University, served as Director of Medical Education and Director of IND/NDA courses for pharmaceutical industry continuing education firms, and guest lectured on topics regarding clinical research and regulatory compliance at institutions and universities around the world.

> the extensive and expensive studies in their Phase 3 program. At this meeting between the sponsor and the FDA, discussions will be based on the protocols to be used in the Phase 3 clinical studies and the overall plan to conduct the Phase 3 program. At this meeting, the Division at the FDA that will review the NDA data recommends strongly what they will expect to see when the sponsor submits the data from the clinical research resulting from the Phase 3 studies. The Phase 3 study results will be key in the FDA's decision in approving or not approving the drug.
>
> (b) *Pre-NDA meeting:* This is the most important meeting in the NDA approval process. Prior to this meeting the sponsor submits to the FDA a synopsis of the results of clinical data based on the outcome of their Phases 2 and 3 research. This preliminary review of this data will give the sponsor and the FDA an opportunity to discuss if the data that the sponsor intends to submit in the final NDA is sufficient for approval. At this meeting, the FDA may recommend to the sponsor that additional research, another type of statistical analysis, or other procedures with the data be conducted before submitting their NDA. These requests are not legal requirements as the FDA does not have the authority to legally require a sponsor to conduct an additional study. However, it must be stated that when the FDA recommends additional clinical studies they base their recommendations on what will aid approval.

45. The sponsor selects which of its officers, employees and consultants will attend meetings with the FDA. There is no limit to the number of persons a sponsor may send. Dr. Guarino explains: "Having consulted with many companies and attended many Pre-NDA meetings at the FDA, attendance at these meetings in smaller companies will usually include the chief executive officer/president, and will almost always include the chief medical/scientific officer, a statistician and an expert consultant who at times is one of the investigators that participated in the study."

46. Pre-NDA meetings and End-of-Phase 2 meetings are formal meetings that occur pursuant to FDA procedures and regulations. Briefing books or synopses of data are provided to the FDA reviewers prior to these meetings. The FDA records meeting minutes to document the discussions and requests made to the sponsor in these meetings. As Dr. Guarino explains,

"promptly after meeting with the FDA, it is standard practice for the sponsor's attendees and consultants, together with any executives involved in the development program who did not personally attend the meeting, to discuss what transpired at the meeting and to draft the sponsor's version of the minutes. Sponsor's minutes are transmitted to the FDA shortly after the meeting so that the sponsor's version of what transpired can be considered by the FDA when the FDA prepares its official minutes, and any discrepancies can be discussed. The FDA minutes are then circulated to the sponsor. They serve as the official record of the meeting and any agreements reached in the meeting."

47. When a sponsor believes it has conducted sufficient well-controlled clinical trials, and believes that those trials demonstrate substantial evidence of efficacy and safety consistent with the FDCA, the sponsor may prepare and file an NDA with the FDA seeking approval to the market the subject drug in a specific dose for the treatment of a specific condition or "indication." The NDA must also specify how the drug will be manufactured, packaged and labeled. The FDA can only grant approval when presented with scientific evidence meeting the requisite statutory criteria.

48. Within sixty (60) days of receiving an NDA, the FDA will accept the NDA for filing if it believes the NDA is sufficiently complete to permit a substantive review of the information contained within the NDA. The acceptance of an NDA for filing is not a determination of the substantive merits of the NDA, but rather a threshold determination of whether there is enough data to conduct a substantive examination. If the FDA determines that there is a facial problem preventing a meaningful substantive examination – for example, if the NDA is missing paperwork, fails to include data in the proper format, or suffers from other facial errors that make review impossible – the FDA may refuse to file the NDA. In AVEO's pre-Class Period

Registration Statement, which was filed with the SEC on Form S-1 on February 23, 2010 and signed by Defendants Ha-Ngoc and Johnston, Defendants conceded understanding that the acceptance of an NDA for filing was only a "threshold determination that it is sufficiently complete to permit substantive review."

49. The filing of an NDA triggers review deadlines specified in the Prescription Drug User Fee Act ("PDUFA"), enacted in 1992 and reauthorized by amendment every five years thereafter. Under the PDUFA, the FDA is generally required to respond to the NDA within six months. The date by which the FDA must issue its response is frequently referred to as a drug's "PDUFA date."

50. An NDA accepted for filing is reviewed for substance by the FDA's Center for Drug Evaluation & Research ("CDER"). Prior to the PDUFA date, CDER may (or may not) convene an advisory committee to provide it with technical advice, enhance its decision-making process, and provide a forum for public discussion of controversial issues.

51. If an advisory committee is convened, the sponsor and the FDA staff will each provide the advisory committee briefing documents and make presentations to the advisory committee. After receiving the submissions of both the sponsor and the FDA, and hearing their respective presentations, the advisory committee will discuss the safety and efficacy of the drug candidate and provide the FDA with a nonbinding vote on specific questions regarding safety and efficacy, and whether approval is warranted based upon the evidence of safety and efficacy provided by the sponsor.

52. Critically, an advisory committee is the only forum in which the public can legally be advised by the FDA of the FDA's position and the FDA's interactions with the sponsor regarding the drug candidate. Except in advisory committee briefing documents and during the

advisory committee hearing, FDA secrecy regulations strictly prohibit the agency from disclosing information regarding pending NDAs. As a result, without an advisory committee, the FDA may not publicly refute a sponsor's misrepresentations regarding clinical trials, protocols, or the sponsor's interactions with the FDA, no matter how false or misleading those statements may be. *See* 21 C.F.R. § 314.430.

Endpoints in clinical cancer studies

53. Safety and efficacy take on particular importance for cancer drugs like tivozanib, because they are generally toxic and can be lethal to patients even if effective in stopping the progress of a disease. Accordingly, trials for drugs intended to treat cancer generally measure both *overall survival*, which measures the length of time from the start of treatment in which the patient remains alive, and *progression-free survival*, the length of time after the start of treatment in which the patient remains alive and the disease, as assessed by study researchers, has not worsened.[4] The difference between *overall survival* and *progression-free survival* is summarized in this chart:

	Overall survival	**Progression-Free Survival**
Permitted by FDA to serve as primary endpoint of Phase 3 clinical trial for renal cell carcinoma?	Yes	Yes, but overall survival is routinely also considered by the FDA in such cases
Method of measurement	Patient death	Mostly radiologic scans of tumor size, and to a much lesser extent, patient death
Cost of sufficiently powering trial to assess statistical significance)	Very expensive	Less expensive
Time required to measure	Significantly more, because measurement cannot be made until patient dies	Much less, because the vast majority of measurement can be accomplished by radiologic scan

[4] *See, generally,* dictionary published by National Cancer Institute for definitions of these and other terms, available at http://cancer.gov/dictionary.

Confounded by subsequent treatment	Yes	No
Involves subjective judgment?	No	Yes

54. Overall survival is considered to be the "gold standard" for clinical trials. Overall survival is an objective, clinical endpoint. However, establishing advantage in overall survival generally requires a larger patient population and takes much longer to assess, because it can only be measured when a patient dies, even if the patient has completed treatment. For these reasons, studies focusing on overall survival tend to be significantly longer and more expensive than those focusing on surrogate endpoints like progression-free survival. Another disadvantage of overall survival is that it can be confounded by subsequent treatments.

55. Progression-free survival, on the other hand, is often favored by drug companies because it can allow for smaller and cheaper trials. For progression-free survival in renal carcinoma, the progression of the disease is assessed at regular intervals using radiologic scans. A patient is considered to have achieved "progression-free survival" if she remains alive and the radiologic scans demonstrate that the tumor has not grown more than a pre-specified amount. Approximately 92% of the progression events-free survival results for the clinical trial at issue in this case were attributable to radiological tumor measurements, as opposed to the actual life or death of the patient.

56. Progression-free survival is considered a surrogate rather than a pure clinical endpoint, because tumor size is correlated with but not a direct measure of survival. As Derek Lowe, a journalist following the pharmaceutical industry, noted: "progression-free survival does not necessarily mean 'survival', not in the sense that cancer patients and their relatives really care about. Dying in the same amount of time, albeit with redistributed tumor tissue, is not the endpoint

that people are waiting for."[5] Another disadvantage of progression-free survival is that it relies on human judgment and assessment, and is therefore prone to bias, especially in open label studies, *i.e.,* studies in which researchers and patients know who receives the study drug and who receives the control or placebo drug. TIVO-1 was an open label study.

57. Because it takes far less time and expense to sufficiently power a clinical trial focusing on progression-free survival than overall survival, the FDA has allowed progression-free survival to serve as a primary endpoint for Phase 3 trials of treatments for renal cell carcinoma. However, the FDA has routinely considered overall survival – the life and death of patients – as a crucial element for approval of renal cell carcinoma treatments, even where progression-free survival was the primary endpoint. As the FDA reiterated in the Advisory Committee Meeting, it has never approved a renal cell cancer treatment demonstrating lower overall survival.

Tivozanib becomes the centerpiece of Defendant Ha-Ngoc's 10-year plan

58. AVEO is a biopharmaceutical company focused on discovering, developing, and commercializing cancer therapeutics. When Defendant Ha-Ngoc joined AVEO in 2002, he committed the Company to a 10-year plan to transform from a development company into an independent integrated pharmaceutical company. Ha-Ngoc described the 10-year plan as his "vision," and stated that it would culminate with AVEO's filing of its first NDA 10 years later in 2012.

59. During Ha-Ngoc's early years at AVEO, the Company pursued many different early-stage candidates with limited success. If Ha-Ngoc was going to have any chance at achieving

[5] http://pipeline.corante.com/archives/2012/08/08/does_aveos_tivozanib_work_or_not.php.

his vision, AVEO would need a breakthrough. AVEO thought it found that breakthrough when it inked a deal in 2006 to license tivozanib from Kirin Brewery Company of Japan.

60. Tivozanib quickly became AVEO's lead product and the focus of its research and development. Tivozanib is an oral inhibitor of the vascular endothelial growth factor ("VEGF") receptors. VEGF is a signal protein produced by cells that stimulates blood vessel creation. When overexpressed, VEGF can contribute to the growth of cancerous tumors, because solid cancers cannot grow beyond a limited size without an adequate blood supply.

61. Drugs which inhibit VEGF receptors have been approved as targeted treatments for renal cell carcinoma since 2005, replacing cytokine therapy such as interferon-alpha and interleukin-2, and systemic therapies such as chemotherapy. Approved anti-VEGF drugs for the treatment of renal cell carcinoma include sorafenib, sutinib, and pazopanib, among others. AVEO sought to gain approval and commercialize tivozanib as a competitor to these established first-line therapies.

62. Defendants, who claimed in their representations to investors to be familiar with and able to speak competently regarding the pivotal clinical trials supporting the approval of other anti-VEGF drugs, knew that no anti-VEGF drug had ever been approved where it showed a higher risk of death, *i.e.*, worse overall survival.

Defendants compromise TIVO-1, AVEO's sole pivotal clinical trial

63. In December 2008 and May 2009, AVEO had formal End-of-Phase 2 meetings with the FDA regarding the design of a Phase 3 pivotal clinical trial for tivozanib, AVEO's first-ever Phase 3 clinical trial. The December 2008 and May 2009 FDA meetings were well-documented and governed by regulation. *See* 21 C.F.R. § 312.47. A primary purpose of these meetings, according to regulation, was to "evaluate the Phase 3 plan and protocols." 21 C.F.R. §

312.47(b)(1). At least one month prior to each meeting, AVEO was required to provide the FDA with a briefing book describing, *inter alia*, "the specific protocols for Phase 3 clinical studies." 21 C.F.R. § 312.47(b)(1)(iv). Additionally, after the meetings, FDA circulated minutes to AVEO which serve as a formal and permanent record of the meetings. 21 CFR. § 312.47(b)(1)(v). Accordingly, at all times relevant hereto, Defendants had in their possession documentation describing the trial design discussed with the FDA, and therefore knew that TIVO-1 was actually conducted in contravention of that design.

64. During the December 2008 and May 2009 meetings, the FDA expressly requested that the Company analyze overall survival of study participants in addition to progression-free survival. In the December 2008 and May 2009 meetings, the FDA agreed that a "substantial, robust improvement" in progression-free survival could be the primary endpoint for the TIVO-1, as had been the case with other renal cancer drugs. Consistent with the FDA's goal of prolonging patient lives, the FDA expressly requested that AVEO include in TIVO-1 a pre-specified plan for analyzing overall survival, and told AVEO that such analysis was "helpful in the regulatory decision making process." Acknowledging the difficulty in powering a study to demonstrate statistically significant improvement in overall survival, the FDA stated that it would not require AVEO to prove a statistically significant improvement in overall survival.

65. At no time did the FDA tell AVEO that it would approve a drug with a higher death rate. To the contrary, as the FDA explained during the advisory committee meeting, "FDA has consistently informed sponsors in meetings and public presentations that while FDA will accept PFS [progression-free survival] as the primary endpoint for certain disease settings, overall survival remains an important efficacy and safety endpoint. PFS may serve as a primary endpoint in trials for practical reasons, but overall survival is considered to be of ultimate clinical benefit."

66. Following the December 2008 and May 2009 meetings, the Company specified a protocol for a Phase 3 clinical trial known as Study 301 and referred to by the Company as TIVO-1. According to the protocol, TIVO-1 was a randomized, open-label comparison trial where the experimental arm was provided tivozanib and the control arm provided sorafenib, an approved treatment for renal cell carcinoma. The protocol for TIVO-1 designated a statistically-significant improvement in progression-free survival as the primary endpoint, and a comparison of overall survival as a secondary endpoint. As the FDA explained in the ODAC advisory committee panel, the pre-specified statistical analysis plan for TIVO-1 indicated a hierarchical analysis of secondary endpoints under which the overall survival comparison was the most important, and analysis of other secondary endpoints was not to be undertaken unless an overall survival benefit was achieved.

67. The TIVO-1 protocol specified that patients would continue to receive either tivozanib (experimental arm) or sorafenib (control arm) for the twenty-four month duration of the trial unless they died or experienced a "progression event," AVEO's jargon for a certain level of tumor growth as measured by radiological scans. Following a "progression event," TIVO-1's protocol, and the design discussed with the FDA, specified no second-line care because such second-line care could confound overall survival results. Accordingly, patients were to go off the study drug and return to the standard of care prescribed by their physicians.

68. The TIVO-1 protocol stated that participants would be enrolled in approximately 90-100 sites worldwide and stratified by geography into three major geographic groups: North American/Western Europe, Central/Eastern Europe, and the "Rest of the World." The pre-specification of geographic stratification reflected Defendants' understanding, at all relevant times, that treatment for renal cell carcinoma varied across geographies. Defendants' understanding that

geographic dispersion was required was also reflected in more than a dozen pre-Class Period SEC filings signed (or certified) by Defendants Ha-Ngoc and Johnston, which each conceded that Phase 3 clinical trials must be "controlled clinical trials conducted in an expanded patient population generally at ***geographically dispersed clinical trial sites.***" (emphasis added). To speed enrollment, lower the cost of TIVO-1, and boost results, Defendants compromised TIVO-1 with three scientifically-flawed shortcuts that were contrary to the study design they discussed with the FDA:

A. One-way crossover: Defendants confounded study results by offering free second-line therapy as an enrollment incentive, and providing it unevenly to only one study arm. This one-way crossover was not included on either the preliminary or final protocols for the TIVO-1 trial, and was not discussed with the FDA. Under the crossover, patients randomized to the sorafenib (control) arm were given the opportunity to "cross over," or switch to tivozanib as a subsequent treatment, without cost. By contrast, patients randomized to the tivozanib arm were not offered any subsidized second-line treatment. Defendants introduced the one-way crossover as a perk to entice and maintain enrollment in TIVO-1, so that patients randomized to receive sorafenib would not leave the trial. As is detailed herein, the FDA has warned and Defendants at all relevant times understood that such one-way crossovers could compromise the ability to assess overall survival. When a patient is crossed over to a subsequent therapy it is difficult and often impossible to determine whether that patient's survival benefit was attributable to the randomized therapy or the subsequent treatment.

B. Extreme geographic concentration: Defendants chose to enroll their test almost exclusively in Central and Eastern Europe, where they knew second-line therapies

were not commonly used for treatment of renal cell carcinoma. This exacerbated the design defect caused by the one-way crossover, because it ensured that patients randomized to the tivozanib arm were unlikely to receive any subsequent targeted therapy, whereas patients randomized to the sorafenib would receive a subsequent therapy – tivozanib – for free. Central and Eastern European study sites also reported adverse events at far lower rates, which can impair the ability to meaningfully assess safety.

C. Biased dose reductions: While both study arms allowed for dose reductions if patients were experiencing adverse reactions, Defendants arranged for the dosages to be reduced at materially different rates. Dosage rates of the control drug, sorafenib, were cut by 50% when the dose was reduced (with the option for investigators to further halve the dosage), whereas rates of tivozanib were only reduced by 33% (with no option for further reduction). As a result, it was unclear whether patients in the sorafenib (control) arm who experienced disease progression after dose reduction did so because of the exaggerated dose reduction, or because there was a difference in the therapeutic effects of the compared drugs. This design defect compromised the progression-free survival results of the study.

69. The defects that Defendants introduced into TIVO-1 were planned and avoidable. Defendants could easily have ensured that the TIVO-1 was enrolled globally as specified instead of clustered in Eastern and Central Europe by capping enrollment by site, or by opening additional sites in the United States and/or Western Europe, but chose not to do so because that could delay the trial and make it more expensive.

70. Proceeding almost entirely in Central and Eastern Europe, although faster and cheaper, introduced a new problem related to drop outs in the control arm. TIVO-1 was unblinded, so patients would know from the outset whether they were to receive tivozanib, a potentially effective experimental drug, or sorafenib, an already-outdated treatment. Investigators worried that Central and Eastern European patients, upon being told they would receive the outdated sorafenib, would drop out of the study, because (unlike in the United States or Western Europe), patients are generally only provided a single line of therapy in those regions.

71. Accordingly, Defendants AVEO, Ha-Ngoc and Slichenmyer changed TIVO-1 to allow patients in the sorafenib arm to *also* receive tivozanib as a free second-line therapy. With this unscientific incentive in place, AVEO was able to speed enrollment and fully enroll TIVO-1 in approximately six months, or nearly half the time it thought enrollment would take.

72. The one-way crossover incentive ensured that there would be unequal therapies between the two arms of the TIVO-1 study, with most patients randomized to the experimental arm receiving no second line therapy and most patients randomized to the control arm receiving both first-line (sorafenib) and second-line (tivozanib) therapies. As Dr. Slichenmyer explained, the decision to render unequal treatment to the two study arms was "a fairly unique situation…. And at – there, at least in RCC [renal cell carcinoma], we don't know of any relevant comparisons. So I think we're in something of an unchartered territory here."

73. Although the one-way crossover incentive radically changed the design of the Phase 3 clinical trial, and Dr. Slichenmyer anticipated that adding the one-way crossover would confound overall survival results, AVEO declined to discuss the crossover with the FDA doctors and staff with whom AVEO met in September 2008 and May 2009 to obtain guidance on Phase 3 trial design. Nor did AVEO file the one-way crossover as an amendment to the TIVO-1 protocol.

Instead, AVEO filed the protocol as a separate "extension" trial, and chose not to discuss it with the FDA. As Dr. Guarino explains, "a sponsor seeking guidance on a protocol should do so by way of a meeting request or a conference call with the FDA, especially where the protocol impacts the design of a study discussed with the FDA at an End-of-Phase 2 meeting." Filing a separate protocol assures only a bare-bones safety review, instead of the meaningful substantive guidance arising from a formal meeting or teleconference. As Dr. Guarino explains, "if a protocol does not present any unforeseen danger to the patient and complies with the dosages set by the Phase 2 results the FDA will not issue a clinical hold on a protocol."

74. AVEO began enrolling participants for TIVO-1 in February 2010 and completed enrollment in August 2010. Contrary to protocol specifications calling for a broad worldwide trial stratified across geographies, AVEO enrolled approximately 88% of TIVO-1 participants in Central and Eastern Europe, where enrollment and testing were cheaper. Because TIVO-1 was an open label study, data was not blinded from the sponsor and the sponsor was able to monitor the progress of the trial at all relevant times.

75. Rapid enrollment for TIVO-1 was critical to AVEO because AVEO was in a race with other companies to develop and commercialize the next generation of anti-VEGF therapies. In particular, AVEO was attempting to outpace Pfizer, which already had the leading approved anti-VEGF therapy, Sutent (sutinib), and was in Phase 3 trials for its next generation anti-VEGF therapy, axitinib. Defendants understood threat posed by Pfizer and others. For example, at the RBC Capital Markets Global Health Care Conference on February 28, 2012, Defendant Johnston agreed that the market for renal cancer treatments was "crowded," and stated for that reason he and AVEO assumed that tivozanib would be on a standard rather than expedited review path with the FDA.

76. The rapid enrollment also inured a personal benefit to Defendants Ha-Ngoc, Johnston and Slichenmyer. The 2010 performance compensation of these Defendants was tied largely to completing enrollment, which was cited in AVEO's Definitive Proxy Statement filed with the SEC on Form DEF 14A on April 18, 2011, as both the Company's most significant corporate goal for all Defendants and an individual goal for Defendant Slichenmyer.

77. In 2011, AVEO entered into a partnership with Astellas Pharma ("Astellas"), a global pharmaceutical company headquartered in Japan, for the development and marketing of tivozanib. Under the agreement, Astellas made a significant cash contribution to AVEO, and agreed to split certain development costs for tivozanib. In exchange, Astellas received a 50% interest in tivozanib. The agreement provided that AVEO would lead efforts to gain approval and market the drug in the United States, while Astellas would lead commercialization efforts in Europe. The agreement also provided AVEO with a financial bonus of $15 million upon the filing of a new drug application with the FDA for tivozanib.

78. In the spring of 2012, AVEO sent the FDA a request for a pre-NDA meeting, which was scheduled for May 11, 2012.

79. On April 27, 2012, AVEO filed its Definitive Proxy Statement with the SEC on Form DEF 14A. The April 2012 Definitive Proxy Statement confirmed that Defendants Ha-Ngoc, Johnston and Slichenmyer continued to receive personal benefits tied to the advancement of the TIVO-1 trial, which was designated as AVEO's most important corporate goal for 2011. Defendant Ha-Ngoc was awarded not only 130% of his targeted cash incentive bonus, but also an additional "one-time" $50,000 cash bonus for "overall leadership" including advancement of the development of tivozanib and the Astellas partnership covering tivozanib, for total cash bonuses of $432,000, and total 2011 compensation of $2,027,545. Defendant Slichenmyer was awarded

not only 128% of his targeted cash incentive bonus, but also an additional "one-time" $20,000 cash bonus for "leadership in overseeing the phase 3 clinical trial of tivozanib", for total cash bonuses of $205,887, and total 2011 compensation of $814,568. Defendant Johnston was awarded not only 128% of his targeted cash incentive bonus, but also an additional "one time" cash bonus of $20,000 for his role in raising additional money from public investors, for total cash bonuses of $187,310 and total 2011 compensation of $760,932.

Defendants learn of higher death rates in tivozanib arm of TIVO-1

80. Higher death rates began to emerge in the tivozanib arm during the first half of 2011, as early as six months after the TIVO-1 trial commenced. By May 2012, AVEO had gathered more than eighteen months of data in TIVO-1, and knew that what initially began as an adverse trend in overall survival had not only continued but worsened. It was clear by this time that patients randomized to the tivozanib arm were dying more frequently than those randomized to the sorafenib (control) arm. Defendants learned this data as the deaths were reported because TIVO-1 was a fully unblinded, open-label study.

Defendants learn that the FDA requested a second Phase 3 trial

81. On May 11, 2012, AVEO had its formal pre-NDA meeting with the FDA regarding the NDA for tivozanib. At that time, and throughout the Class Period, tivozanib was the only advanced-stage (*i.e.,* Phase 3) drug candidate in AVEO's pipeline and, by far, its most important product. According to AVEO's own quantification of its 2012 corporate goals, AVEO considered advancing tivozanib to be more than three times as important as its next most advanced drug candidate, ficlatuzumab, and five times as important as its other pipeline products.

82. Defendant Slichenmyer personally attended the May 11, 2012 pre-NDA meeting. Promptly thereafter, beginning on his return flight home from the pre-NDA meeting, Defendant

Slichenmyer prepared a PowerPoint presentation summarizing the meeting contents and its impact on AVEO. Either that day or the following day, AVEO convened an emergency meeting of its Executive Committee, including Defendant Johnston (who attended in person) and Defendant Ha-Ngoc (who attended by phone). Defendant Slichenmyer provided the Executive Committee with PowerPoint slides summarizing the pre-NDA meeting, and debriefed them on the contents of that meeting. Thus, by May 12, 2012, all of the Individual Defendants herein had actual knowledge of the contents of the pre-NDA meeting.

83. In the pre-NDA meeting, the FDA expressed concern that the Company's sole pivotal clinical trial demonstrated an adverse trend in overall survival. As Defendant Slichenmyer admitted after the Class Period in a June 11, 2013 conference call, the FDA's official minutes from the May 2012 pre-NDA meeting stated:

> The agency expressed a concern about the adverse trend in overall survival. Further discussion of these findings will be required at the time of filing, and if the application is filed, there will be a review issue that could affect approvability. The FDA recommended that the sponsor conduct a second adequately-powered randomized trial in a population comparable to that in the U.S.

AVEO knew about each of these deaths as they occurred, because TIVO-1 was an unblinded, open label trial. Indeed, AVEO was required to monitor patient deaths because it had an obligation to report each death promptly to the FDA. In addition, the FDA warned that the defective design of the TIVO-1 study made it difficult to tell whether tivozanib was "toxic."

84. Defendant Slichenmyer's PowerPoint presentation to AVEO's Executive Committee conceded both the importance of the FDA's request for a second clinical trial, and Defendants' understanding of that importance.

85. It warned that proceeding without the recommended second pivotal clinical trial would ***create a "high risk of…Non-approval."*** Conversely, the same slide acknowledged that

completing a second trial before seeking approval, at least in the United States, would "reduce[] risk."

86. Further reflecting their understanding that a second randomized trial was crucial to tivozanib's prospects for approval, Defendants began designing a second randomized trial called TIVO-2 that would cost $83 million and take approximately three years to complete. Within a month after the May 2012 FDA meeting, Defendants had prepared a draft study protocol and budget, and received approval from the Company's board of directors.

87. Unable to promptly secure the FDA's agreement on the design of a second clinical trial, Defendants took an enormous gamble: they decided to defy the FDA's advice and proceed with an NDA based only on theTIVO-1 trial, despite their actual knowledge that the FDA considered TIVO-1 to be flawed, and its results to be below the standards for approval. However, in their statements to investors regarding the NDA, regulatory communications, and tivozanib, Defendants at least recklessly concealed this game-changing risk.

DEFENDANTS MAKE MATERIALLY FALSE AND MISLEADING STATEMENTS DURING THE CLASS PERIOD

88. The Class Period begins on May 16, 2012, only days after Defendants convened an emergency executive committee meeting to discuss the devastating news received by the Company in the May 11, 2012 pre-NDA meeting. On May 16, 2012, the Company issued a materially misleading press release announcing positive findings from TIVO-1 entitled, "Superiority Study of Tivozanib in First-Line Advanced RCC." The press release announced that in TIVO-1, tivozanib had "demonstrated statistically significant and clinically meaningful progression-free survival (PFS) superiority versus an approved targeted agent (sorafenib) in advanced RCC." The May 16, 2012 press release also announced preliminary information regarding overall survival indicating a one-year overall survival rate of 81% for the sorafenib arm versus 77% for the

tivozanib arm, but strongly encouraged investors to ignore these results by: (a) characterizing them as "preliminary," "interim" and "not mature;" (b) claiming that the disparity was caused by subsequent therapy in the sorafenib arm, when that was merely a hypothesis rather than a proven fact, when in fact the FDA had warned that it was unable to tell whether tivozanib was "toxic"; (c) omitting key regulatory communications expressing concern about overall survival; and (d) omitting that their own scientific misconduct in study design rendered the data uninterpretable.

89. The statements identified in Paragraph 88 above were materially misleading when made because they omitted the following adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA had five days earlier told AVEO that it was concerned about overall survival results; (b) that the FDA had five days earlier requested that the Company conduct a second pivotal clinical trial due to the higher death rates, protocol deviations and scientific misconduct compromising the results of TIVO-1; (c) that the integrity of the TIVO-1 trial was compromised by three defects contradicting the study design discussed with the FDA: an unscientific one-way crossover incentive, extreme geographic concentration of study sites, and biased dose reductions; (d) that the design defects described in (c) were so severe that they rendered the results of the TIVO-1 trial uninterpretable; (e) that as result of design defects in TIVO-1, the FDA found it difficult to tell whether tivozanib was "toxic"; and (f) that the FDA had told AVEO five days earlier that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval

90. Defendants knew or recklessly disregarded that the statements described in Paragraph 88 were materially false and misleading when made, *inter alia,* because: (a) each of the Defendants either personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting

they omitted from investors; (b) each of the Defendants had access to May 11, 2012 PowerPoint presentations acknowledging that failing to complete the requested second pivotal clinical trial would create a "high risk of…Non-approval"; (c) Defendants knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; and (d) Defendants knew that the manner in which TIVO-1 was conducted strayed from protocol and the design discussed with the FDA in End-of-Phase 2 meetings because the FDA had explained the flaws of TIVO-1 in the pre-NDA meeting, and further, Defendants had access to the trial protocols and meeting minutes from the End-of-Phase 2 meetings.

91. The substantial, known risk posed by the FDA's request for a second clinical trial was also the subject of a meeting of AVEO's full board of directors on May 30, 2012. In an additional PowerPoint presentation prepared for that meeting and distributed to Defendants, the Company acknowledged that the FDA had warned at the pre-NDA meeting ***that it would be "in the sponsor's [AVEO's] best interest to start another randomized trial."*** The May 30, 2012 PowerPoint also acknowledged that the FDA told AVEO that "when one randomized trial is used to support registration, ***all endpoints must be consistent."*** Thus, Defendants unquestionably knew in May 2012 that TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval.

92. On June 4, 2012, Defendants AVEO, Ha-Ngoc and Slichenmyer made a presentation to investors related to the data presented by the Company at the annual American Society of Clinical Oncology ("ASCO") meeting. In the presentation, Defendant Slichenmyer regurgitated the Company line that overall survival information was "not sufficiently mature" to discuss and omitted the Company's discussions with the FDA regarding the higher death rate in

the tivozanib arm. In the question-and-answer session, Defendant Slichenmyer was directly asked about whether the geographic mix caused a problem, and misleadingly responded "We don't anticipate that will be a cause of concern to the health authorities."

93. The statements identified in Paragraph 92 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) the Company had already received substantial overall survival data, and while not fully mature it evidenced an unmistakable and worsening trend in overall survival for those patients randomized to the tivazonib arm; (b) the FDA had expressed concern to the Company regarding the adverse trend in overall survival, and sought evidence that the drug itself was not "toxic"; (c) the FDA's concerns were sufficiently significant to raise questions on the agency's part as to whether the Company should even seek approval for the drug; (d) that the Company's ability to ascertain the cause of adverse overall survival data was confounded by the design defects it chose to introduce into the TIVO-1 study, contrary to study protocol and without discussing with the FDA; (e) because of the agency's concerns regarding overall survival and defects in the TIVO-1 trial, the FDA requested that the Company conduct an additional well-designed pivotal clinical trial in a population comparable to the United States; (f) the FDA had already expressed concern regarding the extreme geographic concentration in the pre-NDA meeting; and (g) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval

94. Defendants AVEO, Ha-Ngoc and Slichenmyer knew or recklessly disregarded that the statements described in Paragraph 92 were materially misleading when made, *inter alia,* because: (a) they either personally attended or had actual knowledge of the contents of the pre-

NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they knew that the manner in which TIVO-1 was conducted strayed from protocol and the design discussed with the FDA in End-of-Phase 2 meetings because the FDA had explained the flaws of TIVO-1 in the pre-NDA meeting, and further, Defendants had access to the trial protocols and meeting minutes from the End-of-Phase 2 meetings; (f) they understood that geographic dispersion was important for a well-controlled clinical trial; and (g) they knew that AVEO was in the process of designing and budgeting the second trial requested by the FDA despite the enormous cost and the delay, reflecting their understanding of the importance of the FDA's request.

95. In June or early July 2012, AVEO's board of directors approved a second clinical trial, which AVEO designated TIVO-2. The board of directors budgeted $83 million for TIVO-2, which was expected to take three years to complete.

96. In July 2012, AVEO sent the FDA a formal meeting request to further discuss the second trial and additional analyses of the OS data. The meeting request ***told the FDA that AVEO "<u>will conduct</u> an additional randomized study….as recommended by the Agency at the pre-NDA meeting*** [on May 11, 2012]." The meeting request included a draft protocol for the TIVO-2 study, and asked whether the trial design and a proposed Q1 2013 initiation "are consistent with the

Agency's thoughts regarding an additional RCC [renal cell carcinoma] study mentioned in the pre-NDA meeting."

97. On August 2, 2012, AVEO issued a press release announcing its second quarter 2012 financial and operating results. In this press release, AVEO made a partial disclosure of the regulatory concerns it had received in May 2012. In a paragraph entitled "Regulatory Update," AVEO stated:

> The FDA has expressed concern regarding the OS trend in the TIVO-1 trial and has said that it will review these findings at the time of the NDA filing as well as during the review of the NDA. AVEO is conducting additional analyses to be included in the NDA submission that demonstrate that the OS data from TIVO-1 are consistent with improved clinical outcomes in RCC patients receiving more than one line of therapy; analyses that the company believes will directly address this issue. AVEO is continuing to work toward submitting the NDA by the end of the third quarter; however, there is a chance that the additional OS analyses may cause the submission to move into the fourth quarter.

98. In reaction to the August 2, 2012 partial disclosure, AVEO shares dropped approximately 27% on very high volume, from $13.30 to close at $9.75. The drop, however, would have been much worse had AVEO disclosed the full truth. AVEO was able to limit the decline in its stock price by continuing to conceal the most damaging regulatory communications conveyed during the May 2012 pre-NDA meeting. Namely, Defendants continued to omit that the FDA had recommended a second adequately-powered trial in a comparable population, which the Company acknowledged to be so significant that it had begun to design the trial despite a cost of over $80 million and a three year delay. Defendants also omitted the fact that the FDA had expressed concerns about whether tivozanib was itself "toxic," their understanding that seeking an NDA without a second, well-designed clinical trial disproving such toxicity would create a "high

risk…of Non-approval," and the fact that the Company had already committed to the FDA that it would complete the requested second study.

99. Defendants either knew or recklessly disregarded that the statements described in Paragraphs 97-98 were materially misleading when made, *inter alia*, because: (a) each of the Defendants either personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) each of the Defendants had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they knew that the manner in which TIVO-1 was conducted strayed from protocol and the design discussed with the FDA in End-of-Phase 2 meetings because the FDA had explained the flaws of TIVO-1 in the pre-NDA meeting, and further, Defendants had access to the trial protocols and meeting minutes from the End-of-Phase 2 meetings; (f) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; and (g) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request..

100. To avoid fulsome discussion of their communications with the FDA, Defendants altered a key disclosure in this, and later Class Period periodic report. Prior to the Pre-NDA meeting they directly told investors that they believed FDA discussions supported approval based

on a single clinical trial. Yet, when the FDA told them the exact opposite, Defendants deleted language about their discussions with the FDA regarding the sufficiency of a single clinical trial:

SEC filings before May 11, 2012	SEC filings after May 11, 2012
Based on our discussions with the FDA and the EMEA, we believe we will be required to conduct only a single phase 3 clinical trial of tivozanib in advanced RCC.	[No disclosure of FDA communications regarding the number of clinical trials needed]

101. Defendants also scripted the manner in which FDA communications would be discussed in conference calls. In preparation for investor questions anticipated in a conference call scheduled for August 2, 2012, each of the Defendants participated in a conference call with investors and analysts, ***Defendants AVEO, Ha Ngoc and Johnston drafted a script of questions and approved responses.*** As they expected, Defendant Slichenmyer fielded questions regarding whether the FDA requested additional trials, and he used the scripted answers to keep from investors the FDA's request for a second clinical trial. Defendants, having chosen to portray less than the full truth, were thereby at least reckless as to their propensity to mislead investors.

102. Specifically, analysts on that call expressly asked what studies were requested by the FDA at the pre-NDA meeting, putting each of the Defendants on actual notice that continuing to omit disclosure of the FDA's request for a second pivotal trial was highly likely to materially mislead investors. Just as the script provided, Defendant Slichenmyer dodged the question. Defendants' refusal to provide information regarding whether the FDA had requested one or two pivotal clinical trials was a marked break from their practice prior to the pre-NDA meeting. *See* ¶ 100 for comparison of Pre-May 11, 2012 and Post-May 11, 2012 SEC filings.

103. On August 7, 2012, the Company filed with the SEC on Form 10-Q a quarterly report for the period ending, June 30, 2012. The quarterly report, which was signed by Defendant Johnston and contained a certification signed by Defendant Ha-Ngoc, stated in relevant part:

> Tivozanib, our lead product candidate, the development of which is part of our 2011 partnership with Astellas Pharma Inc., or Astellas, is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor, or VEGF, receptors that is designed to optimize VEGF blockade while minimizing off-target toxicities. Our clinical trials of tivozanib to date have demonstrated a favorable safety and efficacy profile for tivozanib. In May 2012, we announced detailed data from our global, phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment in advanced renal cell carcinoma, or RCC, which we refer to as the TIVO-1 study. The TIVO-1 study is being conducted in patients with advanced clear cell RCC who have undergone a prior nephrectomy (kidney removal) and who have not received any prior VEGF- and mTOR-targeted therapy. In this trial, we measured, among other things, each patient's progression-free survival, or PFS, which refers to the period of time that began when a patient entered the clinical trial and ended when either the patient died or the patient's cancer had grown by a specified percentage or spread to a new location in the body. PFS is the primary endpoint in the TIVO-1 study.

104. The statements identified in Paragraph 103 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the integrity of the TIVO-1 trial was compromised by three defects contradicting the study design discussed with the FDA: an unscientific one-way crossover incentive, extreme geographic concentration of study sites, and biased dose reductions; (b) the design defects described in (a) were so severe that they rendered the results of the TIVO-1 trial uninterpretable, with the FDA warning Defendants that the defective design of the TIVO-1 study made it difficult to tell whether tivozanib was "toxic"; (c) that due to concerns regarding overall survival the FDA had even questioned whether the Company should even seek approval for the drug; and, most importantly, (d) because of the agency's concerns regarding overall survival and defects in the TIVO-1 trial, the FDA requested

that the Company conduct an additional well-designed trial in a population comparable to the United States; (e) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; and (f) Defendants had committed in writing to conducting a second study.

105. Defendants either knew or recklessly disregarded that the statements described in Paragraph 103 were materially false and misleading when made, *inter alia*, because: (a) each of the Defendants either personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) each of the Defendants had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they knew that the manner in which TIVO-1 was conducted strayed from protocol and the design discussed with the FDA in End-of-Phase 2 meetings because the FDA had explained the flaws of TIVO-1 in the pre-NDA meeting, and further, Defendants had access to the trial protocols and meeting minutes from the End-of-Phase 2 meetings; (f) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; and (g) Defendants had caused AVEO's board to consider and approve a three-year, $84 million study, reflecting their understanding of the importance of the omitted second trial request.

106. On August 16, 2012, Defendants AVEO and Johnston made a presentation to investors at the Canaccord Genuity Global Growth Conference, stating in relevant part:

> In sorafenib's pivotal trial, they had a 65% overall survival after the first year. Pazopanib showed 73% overall survival at the one-year timeframe, and Sutent, or sunitinib, showed 78%. In our trial, the tivozanib arm was 77% overall survival. And interestingly, the sorafenib arm showed 81% overall survival. When we met with the FDA in our pre-NDA meeting, this caught their eye, and it's – properly, it's the FDA's job to present safe and effective drugs to the U.S. population. And even though overall survival in this therapy is not an approvable endpoint, this is – the overall survival trend is moving in a different direction than PFS, and they expressed some concern and they would like an explanation. So along those lines, we are doing a lot of analyses to help to address their concern, and we expect to do so as we file our NDA later this quarter.

107. The statements identified in Paragraph 106 above were materially false and misleading when made because overall survival is an approvable endpoint for cancer drugs (though one that AVEO wanted to portray as unimportant because tivozanib's overall survival data was unfavorable), and because the statements omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that when AVEO met with the FDA in the pre-NDA meeting, the FDA requested far more than an explanation – it requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States; (b) due to concerns regarding overall survival, the FDA questioned whether an NDA should be filed at all; (c) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; and (d) Defendants had told the FDA that AVEO "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study.

108. Defendants AVEO and Johnston either knew or recklessly disregarded that the statements described in Paragraph 106 were materially false and misleading when made, *inter alia,*

because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; and (f) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request.

109. On or about August 29, 2012, the FDA sent AVEO a written response to the draft TIVO-2 protocol contained in AVEO's July 2012 meeting request to the FDA. The agency disagreed with the design of TIVO-2: "The FDA has serious concerns regarding the trial design described in your meeting package," in particular its failure to adequately measure OS, which the FDA emphasized as critical given that "the primary concern of the proposed NDA submission is the negative trend in [overall] survival." Defendants did not disclose this letter to investors.

110. Two days later, AVEO responded to the FDA's refusal to rubber-stamp its proposed trial design by canceling the scheduled meeting altogether. It stated: "Upon thorough review, AVEO believes it is not necessary to proceed with this meeting." That same day, AVEO's commercial partner, Astellas, urged AVEO to reconsider its refusal to meet with the FDA, ***warning***

that the issues to be discussed were "directly relevant to the timing and probability for approval…"

111. On September 10, 2012, Defendants AVEO and Johnston made a presentation to investors at the Morgan Stanley Global Healthcare Conference, wherein Defendants were expressly asked about overall survival data and regulatory communications with the FDA, and gave materially misleading answers:

> **Marshall Urist** (moderator)
>
> Okay, great. Well, with that why don't we start, of course, with TIVO and maybe we can chat about some of the – some of your recent discussions with the FDA about the overall survival analyses. So maybe just give a quick overview of the issue for people. And then where are your discussions currently and updated thoughts on this process.
>
> **David B. Johnston**
>
> Certainly. So, this goes back to the design of our Phase III trial, which was a head-to-head or it's the first trial done in the RCC space pivotal trial that used an active targeted comparator, in this case, sorafenib, most of the trials have either used interferon or something like that or even a placebo. So it's tivozanib versus sorafenib. The design of the trial was a one-way crossover. Upon progression if you were initially randomized to the sorafenib arm, you were then eligible and then you progressed, you had confirmed progression. You were then eligible to receive tivozanib following that.
>
> If you were originally randomized on the TIVO arm and you progressed, there was no prescribed crossover, it was the physician's choice or, depending on the geography, best supportive care. And that combined with the geographies where the majority of these sites were, which is mainly Eastern Europe, Ukraine, Russia, Poland et cetera, in many cases, there was no second line therapy or effective second line therapy available for the TIVO arm, whereas on the sorafenib arm, they almost all received TIVO.
>
> So the result of that was when we first went to the FDA in the spring, we just presented top line data for our pre-NDA meeting. What they saw was in the one-year survival percentages of the two arms, those who were randomized to the sorafenib arm, once again those who are eligible to receive TIVO for second line had an 81% survival rate after one year. And those patients who have been originally randomized to the tivozanib arm had a 77% survival rate.

> Now that led the FDA to then say, this is something that we need you to explain, and we expect to see it in your NDA submission and we expect to see from overall survival et cetera. So that's what we're up with the FDA on now.

112. The statements identified in Paragraph 111 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA requested far more than an explanation of adverse overall survival data – it requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States; (b) that Defendants had committed in writing to complete the second test requested by the FDA, but were unable to come up with a scientifically-valid design that would address the FDA's concerns; (c) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; and (d) that AVEO's board of directors had already budgeted $83 million for a second trial, which was expected to take three years.

113. Defendants AVEO and Johnston either knew or recklessly disregarded that the statements described in Paragraph 111 were materially false and misleading when made, *inter alia,* because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they

had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (f) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; and (g) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2.

114. On September 20, 2012, Defendants AVEO and Johnston made a presentation to investors at the UBS Global Healthcare Conference, stating in relevant part:

> **David B. Johnston:**
>
> One of the features of this Phase III trial was a unique one-way crossover design. In the design of this trial, we had input from our principal investigator, Bob Motzer out of Sloan-Kettering, as well as some of the investigators from our Phase II, who strongly suggested that we provide tivozanib to every patient that wants it at some time during the trial.
>
> So we designed a trial that had tivozanib head-to-head versus sorafenib and if you were on the tivozanib arm and you progressed, you were then moved on to the regional standard of care or the physician's choice. The reason that's important is because the region where this trial was primarily done was Eastern Europe. Poland, Ukraine, Russia was the vast majority of the patients. If you were on the sorafenib arm and you progressed, you had the choice and you could be provided tivozanib for second line treatment, or you could choose physician's choice.
>
> If you look at percentage of overall survival after one year that other trials have shown – other pivotal trials, the sorafenib pivotal trial showed 65% of the patients had survived after one year, the pazopanib was 73% and sunitinib or Sutent was 78% in their pivotal trial. For the TIVO-I study, 77% of the patients initially randomized to tivozanib had survived after the 12-month – at the 12-month snapshot. The sorafenib arm showed 81% overall survival. And that was a statistic that was noted at our pre-NDA meeting with the FDA. They were rightly concerned with the fact that the overall survival trends were going in a different direction of PFS. Now at that time, they didn't see any backup analysis.
>
> There was no explanation. They simply said, we need to understand this. And we think that's the right thing.

115. The statements identified in Paragraph 114 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA requested far more than an explanation of adverse overall survival data – it requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States; (b) that the FDA had expressly warned Defendants that the adverse trend could affect approvability, and questioned whether AVEO should even file an NDA; (c) that the design defects Defendants discussed in these statements regarding the TIVO-1 trial, the one-way crossover and the overwhelming focus on Central European and Eastern European patients, were contrary to pre-specified trial protocol and not discussed with the FDA prior to trial initiation; (d) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (e) Defendants had told the FDA that AVEO "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study; and (f) the FDA had criticized the failure of the proposed TIVO-2 study to adequately measure overall survival and refused to rubber-stamp AVEO's proposed second trial.

116. Defendants AVEO and Johnston either knew or recklessly disregarded that the statements described in Paragraph 114 were materially false and misleading when made, *inter alia,* because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse

regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (f) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; and (g) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2.

117. On September 28, 2012, the Company issued a press release announcing that AVEO had submitted an NDA to the FDA seeking approval for tivozanib in patients with advanced rencal cell carcinoma. The press release stated in relevant part:

> The NDA submission is based on results of the global Phase 3 TIVO-1 (Tivozanib Versus Sorafenib in 1st line Advanced RCC) trial, a randomized superiority-designed pivotal trial evaluating the efficacy and safety of tivozanib compared to sorafenib in 517 patients with advanced RCC who had no prior treatment with a systemic therapy, as well as data from 17 clinical studies involving over 1,000 subjects who received tivozanib. In TIVO-1, tivozanib demonstrated a statistically significant improvement in progression-free survival (PFS) versus sorafenib, an approved targeted agent, and a favorable tolerability profile.

118. The statements identified in Paragraph 117 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the integrity of the TIVO-1 trial was compromised by three defects contradicting the study design discussed with the FDA: an unscientific one-way crossover incentive, extreme geographic concentration of study sites, and biased dose reductions; (b) the design defects described in (a) were so severe that they rendered the results of the TIVO-1 trial uninterpretable, with the FDA warning Defendants

that the defective design of the TIVO-1 study made it difficult to tell whether tivozanib was "toxic"; (c) that due to concerns regarding overall survival the FDA had questioned whether the Company should even seek approval for the drug; and, most importantly, (d) because of the agency's concerns regarding overall survival, the FDA requested that the Company conduct an additional well-designed trial in a population comparable to the United States; (e) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (f) Defendants had told the FDA that AVEO "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study; and (g) the FDA had criticized the failure of the proposed TIVO-2 study to adequately measure overall survival and refused to rubber-stamp AVEO's proposed second trial.

119. Defendants either knew or recklessly disregarded that the statements described in Paragraph 117 were materially false and misleading when made, *inter alia*, because: (a) each of them either personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (f) Defendants

had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; and (g) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2.

120. On November 11, 2012, Defendants AVEO and Johnston made a presentation to investors at the Lazard Capital Markets Healthcare Conference, stating in relevant part:

> **Johnston:**
> So the trial was a bit unusual and that it had a one way crossover. This is as far as we can tell on first-line oncology, the first that we can find. There may be others out there, but we haven't been able to find them. So let me describe it to you. If a patient was randomized to tivozanib for first-line and had confirmed disease progression as measured by independent radiological read, they would then move on for second-line treatment, will be the regional standard of care or physician's choice. I'll come back to why that's important in just a moment. If you originally randomize the sorafenib arm and, once again, had confirmed disease progression measured independently, you were then offered a crossover to tivozanib second-line or physician's choice.
>
> The reason why this is important is because this being a first-line VEGF trial, it was done primarily in Eastern Europe, Ukraine, Poland and Russia, where, as it turns out, VEGF TKIs are used with generally for the first-line and they're usually not reimbursed for second-line. And what happened is this. If you look at the left-hand bar here, this is a – this was a cut of patients as of last spring. What you see here is that, at that time, 81 of the patients of the 260 patients on the tivozanib arm were still on first-line therapy. 115 had progressed and had received no – repeat, no second-line therapy, based primarily upon the geographies where they were. 16 had moved on to a VEGF-TKI, which is more and more seen as the most effective second-line therapy. VEGF followed by VEGF is generally seen as the new standard.
> ---
> Now, what that did is when we had our post – our pre-NDA, rather – conversation with the FDA, the FDA saw – this is all that they saw. They didn't see any backup. All they saw was these two numbers. They didn't see any of the breakdown in terms of the second-line therapies or anything like that.
>
> What caught their eye was that this was moving in a different direction than the relative PFSs. So as you recall, in this population, the PFS – so tivozanib, with the intent-to-treat population, was 11.9 months compared to 9.1. Why is this going a different direction? So the conversation we've been having the FDA – and we recently submitted our NDA in late September – September 27. With that, we

> submitted a package explaining with a white paper, showing, first of all, final overall – median overall survival as prescribed by the protocol, as well as a series of analyses supporting the hypothesis that, in fact, TIVO being given to the sorafenib arm as second-line therapy is having beneficial impact.

121. The statements identified in Paragraph 120 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA requested far more than a white paper hypothesizing potential causes of adverse overall survival data – it requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States; (b) that the FDA had expressly warned Defendants that the adverse overall survival trend could affect approvability, and questioned whether AVEO should even file an NDA; (c) that the design defects Defendants discussed in these statements regarding the TIVO-1 trial, the one-way crossover and the overwhelming focus on Central European and Eastern European patients, were contrary to pre-specified trial protocol and not discussed with the FDA prior to trial initiation; (d) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (e) Defendants had told the FDA that AVEO "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study; and (f) the FDA had criticized the failure of the proposed TIVO-2 study to adequately measure overall survival and refused to rubber-stamp AVEO's proposed second trial.

122. Defendants AVEO and Johnston either knew or recklessly disregarded that the statements described in Paragraph 120 were materially misleading when made, *inter alia*, because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted

from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (f) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; and (g) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2.

123. In December 2012, AVEO received its "74-day letter" from the FDA, which expressly stated that ***overall survival remained "a significant safety concern."***

124. On January 8, 2013, Defendants AVEO and Ha-Ngoc made a presentation to investors at the J.P. Morgan Global Healthcare Conference, stating in relevant part:

> [O]verall survival is an important secondary end point that we and others watch and we have disclosed to you the interim analysis at one year showing that in the case of tivozanib patients – randomized tivozanib, shows a 77% overall survival versus an 81% in the control arm, noted also that the difference between two arms is not statistically significant.
>
> However, it's interesting to note that looking across trials that the 77% of tivozanib is among the highest percentage across all the other agents. And that is one of the key feature of our study design that allow for crossover, particularly on the control arms progressor into tivozanib as a companion study.
>
> And let me describe to you the chart here in the bottom half of this slide. It shows that on the right-hand side, the patients who progress on

> sorafenib, of those, 150 of them received effective VEGF therapy and thankfully, all of them, 148, received tivozanib because we provide for free for those who would like to go that way. In comparison, in the patients randomized the tivozanib arm, only 16 patients received effective VEGF therapy, a 1:10 ratio.
>
> So, in essence, when you look at that picture, the overall survival results that I have described in the previous slide is probably a result of a fact that on one hand, on the right-hand side, you have a sequential treatment of two active agents, first sorafenib and tivozanib. And on the left-hand side for tivozanib is essentially a single agent.

125. The statements identified in Paragraph 124 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA expressly requested far more than a hypothesis about what "probably" caused tivozanib-randomized patients to die more frequently than control-group patients – it requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States to provide interpretable *evidence* regarding overall survival; (b) that AVEO had committed to providing that evidence and conducting the second clinical trial, but was unable to design a scientifically-valid protocol to the satisfaction of the FDA; (c) that the FDA had expressly warned Defendants that the adverse overall survival trend could affect approvability, and questioned whether AVEO should even file an NDA; (d) that the FDA had reiterated in its day 74 letter that OS remained "a significant safety concern," and (e) that the design defects in the TIVO-1 trial, including the one-way crossover and the overwhelming focus on Central European and Eastern European patients, ensured a disparity in second-line therapies between the two study arms and were contrary to pre-specified trial protocol and design discussions with the FDA.

126. Defendants AVEO and Ha-Ngoc either knew or recklessly disregarded that the statements described in Paragraph 124 were materially misleading when made, *inter alia*, because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and

therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (f) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; (g) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2; and (h) they had access to the December 2012 day-74 letter.

127. On January 23, 2013, AVEO took advantage of artificially-inflated prices to sell 7,667,050 million shares of AVEO common stock in a public offering at $7.50 per share, raising approximately $53.6 million after underwriting discounts. This capital raise was critical to the Company's future because prior to the capital raise the Company only had sufficient funds to last through the end of 2013, and even that projection assumed that AVEO would receive a $45 million milestone payment from Astellas predicated on FDA approval for tivozanib. *See* Form 10-Q filed with the SEC on November 18, 2012. Moreover, the Company knew that it would require at least $83 million to complete the second tivozanib trial requested by the FDA.

128. On February 13, 2013, following the release of fourth quarter 2012 financial results, Defendants AVEO, Ha-Ngoc, Johnston, and Slichenmyer held a conference call for investors. During that call, Defendants AVEO and Slichenmyer stated as follows:

> Turning now to the overall survival data. What's shown here are the protocol specified final OS results, which are being presented publicly for the first time today. The language in the protocol specified that the final OS analysis was to be conducted at the time that all patients in the study have been followed up for at least two years following randomization. That time corresponded to the date of August 27, 2012 and we've broaden the data to that point.
>
> This analysis was included in the NDA, which was submitted in September. We expect these results to be a subject of discussion at a future ODAC meeting for which we are preparing. The median overall survival in the tivozanib arm is 28.8 months compared with 29.3 months for the control arm. The hazard ratio is 1.25 and there is a non-significant P value of 0.105.

129. The statements identified in Paragraph 128 above were materially misleading when made because they omitted the following material adverse information necessary to make the statements not misleading under the circumstances in which they were made: (a) that the FDA had expressly requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States to provide interpretable evidence regarding overall survival; (b) that the FDA had not only stated that overall survival would be a review issue, but had expressly warned Defendants that the adverse overall survival trend could affect approvability, and questioned whether AVEO should even file an NDA; (c) that while the overall survival was measured as specified in the TIVO-1 protocol, the interpretation of overall survival was fatally confounded because of design defects in the TIVO-1 trial, including the one-way crossover and the overwhelming focus on Central European and Eastern European patients, that ensured a disparity in second-line therapies between the two study arms and were contrary to pre-specified trial protocol and design discussions with the FDA; (d) the FDA had told AVEO that studies like

TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (e) Defendants had told the FDA that AVEO "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study; (f) the FDA had criticized the failure of the proposed TIVO-2 study to adequately measure overall survival and refused to rubber-stamp AVEO's proposed second trial; and (g) Defendants had been told by the FDA in December 2012 that overall survival remained "a significant safety concern."

130. In the question-and-answer portion of the February 13, 2013 conference call, Defendants AVEO and Slichenmyer further dissembled regarding regulatory communications with the FDA focusing on overall survival:

> **<Q - Geoff C. Meacham>:** … on OS, when you guys designed TIVO-1, maybe walk us through the conversation with FDA. Was there any contemplation of overall survival? And then, when you have the Eastern European geographic sort of bias and you know that limited availability of other meds is there, was this something that you guys could have anticipated when you looked at the design of this, either on its own or when you look at other renal cell agents in these same geographies? Thanks.
>
> **<A - William J. Slichenmyer>:** Geoff, Bill here. And at that time, as the study was being designed, there had been precedents with other phase III trials conducted in the same parts of the world that included one-way crossovers. And in general, overall survival benefit has not been proven, and the reason that the FDA and other health authorities use PFS as an endpoint for registration in RCC is because of the recognized impact of confounding with second and subsequent lines of therapy.
>
> ---
>
> **<Q - Salveen K. Richter>:** Thanks for taking my question. Can you remind us exactly what the FDA was looking for in the additional analysis they requested to understand the overall survival curves?
>
> **<A - William J. Slichenmyer>:** So I think the key thing to note is that we remain confident in the data that we've submitted in the NDA and that we are working with the FDA to address lots of questions they're sending to us, it's difficult at this stage in review process for them to

> ask for a lot of additional analysis. Overall, we are feeling very optimistic that things are going to continue to do well. And I should just maybe add that as a general point of company policy, we don't disclose details of our discussions with the health authorities.

131. The statements identified in Paragraph 130 above were materially misleading when made because they omitted material adverse information necessary to make the statements not misleading under the circumstances in which they were made. Specifically, they described relatively innocuous parts of the Company's regulatory communications with the FDA but concealed the most damaging parts, including the facts that: (a) the FDA had expressly requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States to provide interpretable evidence regarding overall survival, not just a *post hoc* analysis to come up with a hypothesis that might explain causation; (b) the one-way crossover and extreme geographic concentration that confounded overall survival results were contrary to the study design discussed with the FDA; (c) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (d) Defendants had told the FDA that AVEO "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study; (e) the FDA had criticized the failure of the proposed TIVO-2 study to adequately measure overall survival and refused to rubber-stamp AVEO's proposed second trial; and (f) Defendants had been told by the FDA in December 2012 that overall survival remained "a significant safety concern."

132. Defendants AVEO and Slichenmyer either knew or recklessly disregarded that the statements described in Paragraphs 128 and 130 were materially misleading when made, *inter alia*, because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting

they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) analysts had directly asked in August 2, 2012 conference calls as well as that February 13, 2013 conference call what additional studies the FDA had requested, putting Defendants on further notice that such information was highly material to investors; (f) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (g) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; (h) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2; and (i) they had access to the December 2012 day-74 letter.

133. On February 27, 2013, Defendants AVEO and Johnston made a presentation to investors at the RBC Capital Markets Global Healthcare Conference, where they responded falsely to a crucial question from an analyst as follows:

> **Adnan S. Butt**
>
> So the company has been pretty upfront about disclosures, disclosing the OS risk et cetera, OS trend as a concern for the FDA.
>
> **David B. Johnston**
>
> Absolutely.

134. The statements identified in Paragraph 133 above were materially false and misleading when made because neither the Company nor Defendant Johnston had been "upfront"

about overall survival risk or their regulatory communications with the FDA regarding overall survival risk. Specifically, Defendants knew but had not told investors or and analysts: (a) that the FDA had expressly requested that AVEO conduct an additional well-designed Phase 3 clinical trial in a population comparable to the United States to provide interpretable evidence regarding overall survival; (b) that the FDA had warned AVEO that overall survival could affect approvability; (c) that the FDA questioned whether the Company should even file an NDA in light of these concerns; (d) that the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (e) that AVEO had told the FDA it would "w[ould] conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (f) that the FDA rejected AVEO's proposed design for a second trial, criticizing its failure of the proposed TIVO-2 study to adequately measure overall survival and refused to rubber-stamp AVEO's proposed second trial; and (g) that Defendants had been told by the FDA in December 2012 that overall survival remained "a significant safety concern." Defendants AVEO and Johnston knew or recklessly disregarded that these misrepresentations had a high likelihood of misleading investors because an analyst request to confirm "upfront" disclosure regarding FDA concerns leaves no doubt that candid disclosure was critical to investors, and because they understood that the omitted matters had substantial impacts on AVEO's business prospects and financial results.

135. On March 11, 2013, the Company filed with the SEC on Form 10-K its annual report for the period ending December 31, 2012. The annual report, which was signed by Defendants Ha-Ngoc and Johnston, stated in relevant part:

> In the TIVO-1 study, tivozanib demonstrated a statistically significant improvement in PFS over Nexavar with a median PFS of 11.9 months for tivozanib compared to a median PFS of 9.1 months for Nexavar in the overall study population. Tivozanib also demonstrated a statistically significant improvement in

> PFS with a median PFS of 12.7 months compared to a median PFS of 9.1 months for Nexavar in the pre-specified subpopulation of patients who received no prior systemic anti-cancer therapy for metastatic disease—a subpopulation that comprised approximately 70% of the total study population.
>
> Overall survival was a secondary endpoint of the TIVO-1 study. The final overall survival, or OS, analysis, as specified by the TIVO-1 protocol, showed a median OS of 28.8 months (95% confidence interval, or CI: 22.5–NA) for the tivozanib arm versus a median OS of 29.3 months (95% CI: 29.3–NA) for the Nexavar arm.

136. The statements identified in Paragraph 135 above were materially misleading when made because they omitted the following material adverse information necessary to make them not misleading under the circumstances in which they were made: (a) that off-protocol design defects in the TIVO-1 trial ensured that the results of TIVO-1 would lack scientific rigor and be uninterpretable with the FDA warning Defendants that the defective design of the TIVO-1 study made it difficult to tell whether tivozanib was "toxic"; (b) that the FDA had recommended a second adequately-powered trial in a comparable population to provide scientifically-valid evidence regarding overall survival; (c) that the agency questioned whether AVEO should even file an NDA; (d) that the FDA had expressly warned that adverse overall survival trends could affect approvability; (e) that even the progression-free survival results were tainted by the employment of materially different dose reductions ensuring that the effective dose of the control drug, sorafenib, was reduced far more in a dose reduction event than the experimental drug, tivozanib; (f) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (g) Defendants had told the FDA that AVEO "will conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting" and included a draft protocol for the proposed TIVO-2 study; (h) the FDA had criticized the failure of the proposed TIVO-2 study to adequately measure overall

survival and refused to rubber-stamp AVEO's proposed second trial; and (i) Defendants had been told by the FDA in December 2012 that overall survival remained "a significant safety concern."

137. Defendants AVEO, Johnston and Ha-Ngoc either knew or recklessly disregarded that the statements described in Paragraph 135 were materially misleading when made, *inter alia*, because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a substantial impact on AVEO's financial results and business prospects; (e) analysts had directly asked in August 2, 2012 conference calls as well as that February 13, 2013 conference call what additional studies the FDA had requested, putting Defendants on further notice that such information was highly material to investors; (f) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (g) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; (h) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2; and (i) they had access to the December 2012 day-74 letter.

138. On March 8, 2013, AVEO submitted a meeting request which: (a) submitted a revised protocol for TIVO-2; and (b) asked for the first time whether the study could be done after approval as a "postmarketing commitment or requirement."

139. On or about March 13, 2013, the FDA responded in writing to AVEO's renewed meeting request, stating that the revised protocol was also deficient. It encouraged AVEO to "design the trial properly as soon as possible," and expressly rejected AVEO's request to conduct the trial on a post-approval basis.

140. On March 13, 2013, Defendants AVEO and Johnston made a presentation to investors at the Barclays Capital Global Healthcare Conference, stating in relevant part:

> And lastly and most importantly for us, we need a favorable risk benefit profile. So, if you're here, you probably know that PFS is the accepted registration endpoint for advanced RCC. That's what all the other drugs have been approved on. OS is a secondary endpoint and is often [ph] confounded (5:17). In fact, it's – no drug has shown statistical improvement in overall survival even versus a placebo. The only exception would be the mTOR inhibitor TORISEL in poor prognosis patients, but none of the VEGF TKIs had.
>
> In ours, we had a median OS compared to Sorafenib that had a 28.8 months median compared to 29.3 months on the Sorafenib arm, but it has a ratio of about 1.25 favoring the Sorafenib arm. So, what's going on? If you can see here on the bottom, too – there's a pointer here somewhere, but along the bottom you can see the percentage of patients on the control arm who would cross over to Tivozanib. The reason why this is important is because the design of the trial was such that there was a one way crossover so if you are on Sorafenib arm and you progressed, you got Tivozanib. If you are on the Tivozanib arm and you progress, you just got stay into the care and the geography where the trial is being conducted. So, you can see that towards the end of the trial, over 2/3 of the patients had transferred over to Tivozanib.

141. The statements identified in Paragraph 140 above were materially misleading when made because they omitted the following material adverse information necessary to make them not misleading under the circumstances in which they were made: (a) that off-protocol design defects in the TIVO-1 trial ensured that the results of TIVO-1 would lack scientific rigor and be

uninterpretable; (b) that none of the referenced trials for other approved drugs demonstrated the same safety risk regarding overall survival as tivozanib; (c) that the FDA had recommended a second adequately-powered trial in a comparable population to provide scientifically-valid evidence regarding overall survival; (d) that the agency questioned whether AVEO should even file an NDA; (e) that the FDA had expressly warned that adverse overall survival trends could affect approvability; (f) that even the progression-free survival results were tainted by the employment of materially different dose reductions ensuring that the effective dose of the control drug, sorafenib, was reduced far more in a dose reduction event than the experimental drug, tivozanib; (g) the FDA had told AVEO that studies like TIVO-1, which had inconsistent results in its endpoints, did not satisfy FDA requirements for single-trial approval; (h) Defendants had told the FDA that AVEO "will conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (i) the FDA had on two occasions rejected proposed trial protocols for the second trial due to design deficiencies; and (j) Defendants had been told by the FDA in December 2012 that overall survival remained "a significant safety concern."

142. Defendants AVEO and Johnston either knew or recklessly disregarded that the statements described in Paragraph 140 were materially misleading when made, *inter alia*, because: (a) they personally attended or had actual knowledge of the contents of the pre-NDA meeting, and therefore knew of the material adverse regulatory communications in that meeting they omitted from investors; (b) they had access to pre-NDA meeting minutes confirming the material adverse regulatory communications in that meeting they omitted from investors; (c) they had access to the May 12, 2012 and May 30, 2012 PowerPoints confirming the material adverse regulatory communications they omitted from investors, and the significance of those communications; (d) they knew that fulfilling or rejecting the FDA's request for a second clinical trial would have a

substantial impact on AVEO's financial results and business prospects; (e) analysts had directly asked in August 2, 2012 conference calls as well as that February 13, 2013 conference call what additional studies the FDA had requested, putting Defendants on further notice that such information was highly material to investors; (f) they had access to AVEO's July 2012 meeting request committing to "conduct an additional randomized study….as recommended by the Agency at the pre-NDA meeting"; (g) Defendants had caused AVEO's board to consider and approve a three-year, $83 million study, reflecting their understanding of the importance of the omitted second trial request; (h) they had access to the FDA's August 29, 2012 letter to AVEO, and therefore knew that the FDA had already rejected the proposed design of TIVO-2; (i) they had access to the December 2012 day-74 letter; and (j) they had access to the March 13, 2013 letter from the FDA.

143. On April 26, 2013, AVEO filed its Definitive Proxy Statement with the SEC on Form DEF 14A, which indicated that Defendants Ha-Ngoc, Johnston and Slichenmyer continued to gain personal economic benefits from the claimed advancement of the tivozanib program. Advancing the tibozanib program was identified as AVEO's most important corporate goal in 2012. All of Defendant Ha-Ngoc's cash incentive bonus was tied to realizing AVEO's corporate goals, including most prominently the goal of advancing the tivozanib program, and 80% of the cash incentive bonuses of Defendants Johnston and Slichenmyer were tied to such goals. Notwithstanding the FDA's sharp criticism of AVEO's only pivotal clinical trial for tivozanib, AVEO's board claimed that the goal of advancing tivozanib was 95% achieved in 2012. As a result, Defendant Ha-Ngoc received a cash incentive bonus of $339,625 and total 2012 compensation of $2,364,483. Defendant Johnston received a cash incentive bonus of $129,142

and total 2012 compensation of $1,002,349. Defendant Slichenmyer received a cash incentive bonus of $148,012 and total 2012 compensation of $1,034,829.

THE TRUTH IS REVEALED

144. On April 30, 2013, the FDA released its ODAC Briefing Document, which disclosed for the first time that the FDA had expressly recommended that the Company conduct an additional clinical trial and highlighted the regulatory history of tivozanib previously concealed by the Company, including the fact that the Company disregarded FDA recommendations for an additional clinical study, "[a] pre-NDA meeting was held in May 2012. Here, the FDA expressed concern about the adverse trend in overall survival in the single Phase 3 trial and recommended that the sponsor [AVEO] conduct a second adequately powered randomized trial in a population comparable to that in the US."

145. The Briefing Document also disclosed that the conduct of the TIVO-1 trial deviated significantly from the design specified in trial protocol and discussed with the FDA in meetings in December 2008 and May 2009. Specifically, the TIVO-1 trial protocol did not include the one-way crossover that Defendants claim confounded overall survival results, and Defendants had not discussed introducing that design defect with the FDA in TIVO-1 design meetings. Moreover, the TIVO-1 trial protocol called for global enrollment rather than biasing study sites to Central and Eastern Europe:

> The Phase 3 study was carried out at 76 sites. It was initiated in February 2010 and was ongoing at the time of submission. As shown in Table 5, *most of the study sites were in Eastern Europe with potentially different standard of care and practice patterns compared to the US.* Patients on the sorafenib arm of the Phase 3 study with PD could receive tivozanib on an extension/crossover study. Patients on the tivozanib arm of the Phase 3 study with PD could receive additional medications. *However, the 2nd line use of targeted therapies was not considered the standard of care in many of the countries participating in the trial.*

Table 5: Geographic Distribution of Patient Accrual

Geographic Region	Tivozanib N = 260	Sorafenib N = 257
Central/Eastern Europe	229 (88%)	228 (89%)
North America/Western Europe	22 (9%)	18 (7%)
Rest of World	9 (4%)	11 (4%)

> The majority of the patients on the sorafenib arm received tivozanib after the development of INV-determined PD while most of the patients on the tivozanib arm did not receive subsequent targeted therapy. *The majority of patients were enrolled from sites in Central and Eastern Europe where 2nd line targeted therapy was not available. This is not consistent with the practice patterns in the US and it is, therefore, unclear whether the patients in this study were representative of those in the US.*

(emphasis added).

146. The Briefing Document also disclosed flaws in the unproven hypothesis Defendants had offered to investors to assuage investor concerns regarding overall survival – that (according to Defendants) the adverse overall survival results for tivozanib were necessarily caused by differing post-study treatments for patients randomized to sorafenib in the TIVO-1 trial, not long-term risks of tivozanib use. As the FDA noted, subsequent therapies had also been introduced in many of the trials for the seven targeted treatments it had already approved for renal cell carcinoma, but the pivotal studies for those drugs all demonstrated overall survival trends in favor of the candidate drug (unlike tivozanib).

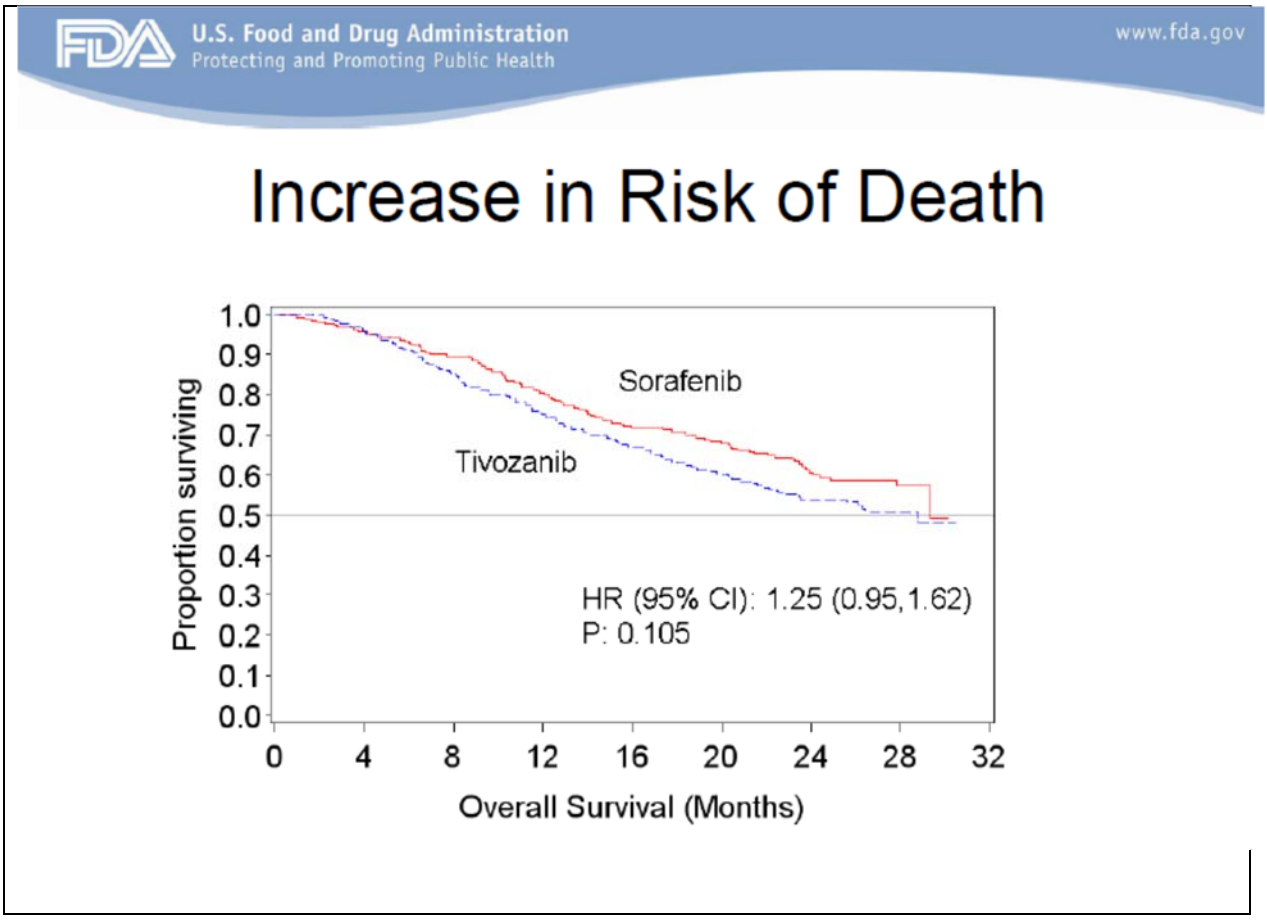
147. In response to the disclosures in the Briefing Document, the Company's shares fell $2.33, or 31.31% per share, to close at $5.11 on April 30, 2013, on volume of over 15 million shares. An article in the Boston Globe confirmed that the decline was due to the new information concealed during the Class Period regarding the FDA's May 11, 2012 request for an additional clinical trial:

> Shares of AVEO Pharmaceuticals Inc. plummeted more than 30 percent Tuesday after the Food and Drug Administration said another

> clinical trial may be needed to weigh the risks and benefits of the Cambridge company's kidney cancer treatment.[6]

148. In the May 2, 2013 hearing before the ODAC panel, the FDA disclosed further information about the regulatory communications and scientific misconduct that the Company had concealed during the Class Period. Indeed, Dr. Ibrahim, Deputy Director of the FDA's Division of Oncology Products 1, explained that the ODAC panel was convened in order to address the agency's concerns regarding higher risk of death (lower overall survival) for tivozanib patients: "Why are we here for this morning's session at ODAC? We are here because we would like to discuss with you a trial that has been submitted, which has shown a concerning increase in the risk of death from the investigational drug tivozanib." According to the FDA, this higher risk of death was indicated by an industry-standard Kaplan-Meier curve which showed "a 25 percent potential increase in the risk of death with tivozanib as compared to sorafenib." The Kaplan-Meier curve, included on the slide reproduced below that the FDA used at the ODAC panel, demonstrated a higher risk of death for tivozanib patients early in the trial, and broadening as time progressed:

[6] R. Weisman, "Shares of AVEO Phamaceuticals plummet as FDA weighs new clinical trial for kidney cancer drug," *Boston Globe*, April 30, 2013.



149. ODAC panel member Dr. Serekes pointed out, and Defendant Slichenmyer was forced to acknowledge in response, that the adverse overall survival trend between tivozanib and sorafenib was evident within six months after treatment began. Accordingly, there is no legitimate basis to believe that the adverse trend was not well known to AVEO and its executives at all times during the Class Period, which begins ***eighteen months*** after TIVO-1 trial commenced enrollment.

150. Dr. Jarow, the FDA's lead presenter, explained why the agency wanted to assess overall survival, as the agency made clear to Defendants in December 2008 and May 2009:

> Why do we care so much about overall survival? Progression-free survival is a composite endpoint of disease progression measured by radiological scans and death. An improvement in progression-free survival of a certain magnitude may be a clinical benefit in and of itself for renal cell carcinoma.

> In this study, 92 percent of the progression events were radiological. In other words, there were very few deaths during the actual study. PFS and OS endpoints are often aligned. Overall survival captures both the efficacy and toxicity of a drug. However, the two endpoints may not always be aligned, such as when drugs have increased toxicity. Therefore, we depend on overall survival to assess the risk/benefit profile of a drug.

151. Dr. Arrington, who led the FDA's presentation on safety at the ODAC panel, explained that tivozanib demonstrated a higher risk of death no matter how the data was sliced, and that the risk may be attributable to lasting effects of tivozanib's toxicity:

> As was presented previously, this slide shows the Kaplan-Meier curves for overall survival, showing a 25 percent potential increase in the risk of death on the tivozanib arm. This is clearly a concerning efficacy and safety finding in this study.
>
> Here we see that regardless of how one approaches the data on deaths in this phase 3 trial, there were more deaths on the tivozanib arm than there were on the sorafenib arm. For death within 30 days, there were more deaths attributed to progressive disease on the tivozanib arm. But, as we know, attribution may be unreliable, especially in an unblinded trial.
>
> When we looked at the number of adverse events reported by region, we saw that there are marked regional differences in the number of patients reporting a grade 3 to 4 adverse event. There were 88 percent and 75 percent reporting a grade 3 to 4 adverse event in North America, Western Europe, and other countries versus the 59 percent in the Central and Eastern European region.
>
> Again note that the majority of patients were enrolled in Central and Eastern Europe, 456, and that the number of patients recruited in the other two regions is small, 60 patients in total. With this small number of patients, we cannot draw firm conclusions concerning regional differences.
>
> The differences observed could be due to the differences in toxicities, experienced as a result of the characteristics of the patient population, or there may be differences in ascertainment or reporting bias. Certainly, this finding does make us question the applicability of the adverse event profile obtained in this study to the U.S. population.

152. Dr. Ibrahim of the FDA emphasized that sponsor companies developing oncologic drugs were consistently warned that overall survival was an important measure for approval even where progression free survival was a primary endpoint:

> FDA has consistently informed sponsors in meetings and public presentations that while FDA will accept PFS as the primary endpoint for certain disease settings, overall survival remains an important efficacy and safety endpoint. PFS may serve as a primary endpoint in trials for practical reasons, but overall survival is generally considered to be of ultimate clinical benefit.

153. In contrast to Defendants' Class Period attempts to portray tivozanib's overall survival data as unremarkable or expected, Dr. Ibrahim made clear that the agency had never before approved a similar treatment that showed inferior overall survival: "Multiple drugs have been approved for metastatic renal cell cancer, but none of them had this concerning issue. In fact, no approved oncology drug has raised this kind of concern for a detriment in survival in recent trials that served as a basis for marketing approval."

154. Critically, Dr. Ibrahim explained that Defendants' attempt to guess at the reason why tivozanib patients experienced a higher risk of death simply was not clinical evidence upon which an approval could be based:

> In the NDA submission and the briefing document, the applicant provides an imbalance in post-study therapy as the reason for inconsistency between PFS and overall survival.
>
> It is possible that tivozanib is an effective drug, and the sequential use after sorafenib improved survival on the sorafenib arm. But there may be other reasons as well, and these include that sorafenib is superior compared to tivozanib in terms of overall survival, and the very real possibility that death from toxicity contributed to a worse survival on the tivozanib arm.
>
> FDA requires adequate and well-controlled studies for approval. This study was not well-controlled for post-study treatments. In addition, consideration should be given to false positive rates when these rationales and other post hoc analyses are assessed. The various post hoc analyses were done in non-randomized populations, and drawing any inference from them is problematic.

> The inconsistent PFS and OS results and imbalance in post-study treatments made the trial's results uninterpretable and inconclusive when making a risk/benefit assessment necessary for approval of a drug.

155. Dr. Jarow of the FDA confirmed that Defendants' rationale for the higher death rates was "just a hypothesis" not proved by evidence:

> The key issue with this application is the inconsistent findings in this single phase 3 trial. A 20 percent benefit in progression-free survival was observed against an active comparator, sorafenib, but we also observe a potential 25 percent increase in the risk of death.
>
> The applicant presents a hypothesis that this is due to confounding by an imbalance in subsequent treatment. However, this cannot be proven based on post hoc exploratory analyses and remains just a hypothesis.

While Dr. Jarow allowed that Defendants' unproved hypothesis might be a "potential cause" of the higher death rates under tivozanib, he noted the hypothesis was inconsistent with evidence from other trials in approved drugs that had previously been published and were known to those conducting research in the field of renal oncology, including Defendants:

> The applicant hypothesizes that the imbalance in subsequent therapy was the cause for the observed decrement in overall survival. However … five of the seven currently approved targeted agents allowed unilateral crossover for their control arm in their pivotal trials, with a rate ranging from 4 percent to as high as 80 percent.
>
> Where data were available, the relative rate of subsequent targeted therapy, which includes both crossover and subsequent therapy given off protocol, was compared for the two arms of each trial. As you can see, there was a significant imbalance in other trials, yet none of these trials demonstrated a negative trend for overall survival.

156. Dr. Pazdur, Director of the FDA's Hematology and Oncology Products' Office of New Drugs, clarified that defects in TIVO-1 made it impossible to tell whether given patient deaths were caused by drug toxicity, disease or other factors:

> We have a study here, basically, and we talking about attribution of death, which is very, very difficult to say why a patient dies, especially when you're dealing with toxicities such as MIs, arterial thrombosis, potential cardiovascular events. We also have an issue of the study

> being conducted largely outside of the United States with sites that we are unfamiliar with. And secondly and most importantly, this trial is unblinded.
>
> So to try to make some type of statement that we know why this patient died, whether it's from disease or from a drug toxicity is very, very, very confounded.

Dr. Pazdur indicated that these trial defects made it impossible for the FDA to determine whether tivozanib caused greater harm than benefit:

> If I could summarize our biggest fear here, it could be summarize by a statement, do no harm.
>
> ***
>
> We have a difference, a modest difference, in progression-free survival, but almost an equally negative impact on overall survival -- rather, a negative impact on overall survival and a positive impact on progression-free survival. And obviously, overall survival is a much more important clinical endpoint than progression-free survival.

157. Dr. Jarow also criticized the confounding of data caused by Defendants' "flaws in the design and conduct of the phase 3 trial, 301 [TIVO-1]." Specifically, he stated:

> The trial design is problematic for employing unilateral crossover in the setting of an active comparator and for performing the trial in a region where there is limited access to subsequent therapies. This is a potential cause of the confounding of the survival data, and also limits the applicability of these trial results to the U.S. population.
> Less than 10 percent of the patients were recruited from Western Europe and North America, and only 16 out of the 517 patients in the study were from the U.S. We will show you that there are differences in the subsequent care based on region that influences the interpretation of the trial, and again, the applicability of the results to patients in the U.S…. All of this [subsequent care] was off protocol.

158. Dr. Dodd, a member of the ODAC panel and a statistical expert at the National Institute of Health, also strongly criticized the defective crossover design:

> So this is a textbook example of why we recommend against crossover. We don't know whether sorafenib worked well and tivozanib didn't, or whether tivozanib worked well, or whether the survival signal is just noise.

> I would have advised strongly against crossover, and if it was deemed absolutely necessary from an ethics perspective, then I would have recommended against allowing the one-way crossover. So this saddens me because we want to speed up the drug development process, but when a trial is poorly conducted, we get fuzzy answers.
>
> The crossover in this case and the way it was conducted -- it was one-sided going from the tivozanib, the experimental arm, or from the sorafenib arm to the tivozanib -- brings up a question for me about the integrity of the progression-free survival result.

159. Dr. Logan, a biostatistical expert on the ODAC panel, explained that the defective trial evidence presented by AVEO fell far short of the requirement for approval:

> Approval based on a single unblinded trial, which is what we have here, really needs robust and statistically compelling and internally consistent evidence of clinical benefit.
>
> What do we have? We have modest evidence of an effect on a radiologic endpoint of progression-free survival; a marginally significant p value of .04, which in the context of typical approvals, which require two studies to be significant is not statistically convincing.
>
> We have potential concerns about a couple issues related to potential bias in the progression-free survival endpoint; effective dose reductions on sorafenib, as well as potential informative censoring, as discussed by Dr. Dodd.
>
> We also have an inconsistent effect on overall survival. In general, I think, as has been alluded to in several points, we have a poor trial design for considering the impact on survival. And survival is very important safety consideration. The use of crossover, and in particular the use of this one sided crossover, really makes the overall survival results very difficult to interpret.
>
> There have been a number of hypotheses that have been proposed for why there may be this adverse impact, but these are all hypotheses.

160. Defendant Slichenmyer, in response to pointed questions from ODAC panel members, reluctantly admitted that the Company implemented the one-way crossover after TIVO-1 had commenced, without discussing with the FDA:

> Crossover was not built into the study as it was initially conceived and discussed with health authorities here, with the FDA and with CHMP. It was only after moving ahead towards implementation of the study,

> talking with investigators at study sites, that they said that they really wanted the study to be designed in a way so that all of their patients could have access to tivozanib.

Defendant Slichenmyer also admitted that he and AVEO had "anticipat[ed]" that the off-protocol crossover might distort overall survival. When pushed, Defendant Slichenmyer further conceded that the analyses the Company included in the NDA to attempt to attribute the higher deaths under tivozanib to this distortion were themselves "post hoc and potentially biased."

161. Dr. Motzer, the Chief Investigator hired by AVEO for the TIVO-1 trial, explained that the crossover was implemented at investigator request for economic purposes, to disincentivize patients from leaving the trial if they were randomized to the sorafenib arm (which would be known because the trial was unblinded and open label):

> So the investigators were somewhat concerned, in an environment where there was multiple drugs, that patients would not go on and stay on if they received sorafenib; if they were registered to sorafenib, that they might drop out and say, I don't really feel like going to this center. I'll go elsewhere.

162. The FDA's Dr. Pazdur also rejected any notion that high enrollment rates in Central and Eastern Europe (enticed, as AVEO's Chief Investigator admitted in Paragraph 161 above by the offer of free post-study treatment as a "crossover") were somehow outside the control of the sponsor. Instead, as Dr. Pazdur explained, the sponsor can always add sites to ensure the global distribution specified in the protocol:

> DR. PAZDUR: I'll answer your question with a question. Why was this trial done only exclusively in Eastern Europe? What was the motivating factor behind it? Was it solely accrual? Were there financial reasons? I don't know. But why was the study solely done in Europe?
>
> If you're telling me that this is such a special drug that we have here that's so much better than everything else, one would think that U.S. investigators would be chomping at the bit to be studying this drug.
>
> So my answer to you, or my question to you, is why is the trial only being done in Eastern Europe?

> DR. FINGERT: I think it actually wasn't, Dr. Pazdur. It was not intentional, and it certainly was not restricted to Eastern Europe for the sponsor.
>
> DR. PAZDUR: I realize that. But on the other hand, when people see their accruals and their patterns of accrual, they can step in to increase the number of sites.

163. Dr. Fojo, a member of the ODAC panel and Program Director for Medical Oncology at the National Cancer Institute, emphasized that the PFS advantage claimed by AVEO may have been caused by materially different dose reduction rates:

> There's something in the study design that I think is concerning to me. The dose adjustment for sorafenib was quite steep. It was a 50 percent reduction, from 400 b.i.d. to 400 q.d. The dose adjustment for tivozanib was only a third, from 1.5 to 1.
>
> So if I were setting up a study, I wouldn't set up such a discrepancy between the two drugs, that I would take my comparator and reduce it by 50 percent in response to toxicity as opposed to only a third for my active agent.
>
> I'm not quite sure there wasn't a 400/200 step along the way. Certainly, I think Dr. Motzer thinks that 400 q.d. of sorafenib is not a very effective drug, so when you reduce it to that, you're actually making it such that the comparator is at a disadvantage.

Dr. Fojo noted that the dose reduction bias likely played a significant role in shaping results because "50-some-odd percent of the patients [in the sorafenib arm] had a dose reduction."

164. Citing defective trial design and conduct, and the lack of evidence explaining the cause of shortened life among tivozanib patients, all of the members of the panel but one voted against recommending approval. A doctor on the panel described his vote as follows:

> I couldn't imagine sitting down and telling a patient that I was going to put them on a drug where the critical trial showed that it would actually shorten their survival.

Similarly, another explained:

> [T]he design of the study is simply inadequate, especially given that only one phase 3 study has been conducted. And in the sponsor's own words, the single phase 3 study was a comparison of single-line therapy versus those who received two lines of therapy.

> ***
>
> The amount of time that the sponsor had expended in explaining away the overall survival difference would have been better spent in conducting a better-designed study. Not having done that, we are left to guess and speculate on why the overall survival is going in the wrong direction for tivozanib.

Another summarized:

> I think if this trial had been conducted in a better way in terms of the design specifically, that we might not be here.

165. As a result of the additional adverse information disclosed in the ODAC hearing, AVEO shares declined $2.61 per share to close at $2.65 per share on May 2, 2013. This drop of nearly 50% was on massive volume of over 15 million shares.

Post-Class Period Reaction

166. Analysts and press also reacted strongly to AVEO's scientific misconduct and failure to come clean with investors. For example, in a May 6, 2013 article published in *TheStreet.com*, senior pharmaceutical correspondent Adam Feuerstein wrote:

> The committee's response was unequivocal: There is no compelling evidence, largely because AVEO conducted a flawed clinical trial.
>
> Worse, AVEO knew it had a problem well before last Thursday's FDA panel meeting. The FDA told AVEO last May that a second clinical trial should be run. AVEO ignored that advice and didn't disclose the recommendation to anyone. There's your arrogance.

167. On or about May 24, 2013, Astellas revealed that it would not fund additional clinical trials for tivozanib as a treatment for kidney cancer, and would not seek approval in Europe for tivozanib as a treatment for kidney cancer.

168. On June 11, 2013, AVEO conducted a conference call to discuss a complete response letter it had received from the FDA, rejecting its NDA for tivozanib. In the conference call, Defendants Slichenmyer and AVEO conceded they had known since May 2012 that the FDA wanted to see an additional clinical trial but had disregarded that advice:

> Since ODAC, we have received questions about FDA's recommendation for a second study. Let me walk you through our thinking on that and provide some context. Let's start with the pre-NDA meeting we had in May of 2012. At that meeting, we discussed with the agency the results from an interim analysis of overall survival, along with other efficacy and safety data.
>
> The agency expressed concern about the adverse trend in OS. Directly from the FDA's minutes from that meeting I quote, "The agency expressed a concern about the adverse trend in overall survival. Further discussion of these findings will be required at the time of filing, and if the application is filed, there will be a review issue that could affect approvability. The FDA recommended that the sponsor conduct a second adequately-powered randomized trial in a population comparable to that in the U.S." At that time, the agency requested that the NDA submission include the results from the final OS analysis, which was expected sometime after August 2012.

169. In the June 11, 2013 conference call, Defendants also admitted that the FDA ***had not*** agreed to Defendants' request to conduct the second clinical trial as a post-approval study:

> **<Q - Adnan S. Butt>:** Sure. So I have two questions. First, from the events that transpired it seemed that the FDA wanted a second study, but the company went ahead and filed regardless of the FDA's communication. Did AVEO ever directly ask the FDA if a second study was needed? That's the first question. And then in terms of the second question, will the outcome of this decision, has it impacted enrollment in the ongoing studies in any way?
>
> **<A - William J. Slichenmyer>:** So in terms of did we directly ask the agency if another study was needed, what we did ask was whether or not or in what way this request for another study might impact the file-ability of our NDA. And we did not get a clear answer prior to the submission on that question other than for them to say that they would evaluate it at the time of their filing decision and, as we now know, they accepted the NDA for filing. We have subsequently suggested a couple of times to the agency that we viewed this as a post-approval study and ***the agency did not commit to agreeing with that*** or to disagreeing with that. [emphasis added].

170. On July 3, 2013, AVEO received an investigational subpoena for documents at AVEO "concerning tivozanib" and also "including related communications with the FDA, investors and others." AVEO later admitted in an SEC filing that it had received the subpoena,

but has not released the actual subpoena or its communications with the SEC regarding the investigation. The fact that a subpoena was issued alone indicates that the investigation is formal rather than informal. The SEC only issues investigational subpoenas as part of formal inquiry into potential violations of federal securities laws.

171. An August 13, 2013 article from Chris Rees that was published in *TheStreet.com* criticized Defendants for withholding the adverse information identified herein regarding their May 2012 regulatory communications with the FDA:

> In my view, this was material information that should have been fully disclosed to investors….
>
> It appears AVEO knew this OS data was a bigger issue for the FDA than what shareholders were told. It also appears that AVEO knew the possibility (or probability) of the FDA requiring a new OS trial was greater than they led investors to believe.
>
> If the information disclosed (for the first time) in [a post-Class Period conference call] had been made public prior to AVEO's ODAC meeting, investors who lost money may have decided to reduce or limit the size of their investment, or may have decided not to invest in AVEO at all.[7]

CLASS ACTION ALLEGATIONS

172. Plaintiffs bring this action as a class action pursuant to Federal Rule of Civil Procedure 23(a) and (b)(3) on behalf of all those who purchased or otherwise acquired AVEO common stock between May 16, 2012 and May 1, 2013, both dates inclusive (the "Class"); and were damaged thereby. Excluded from the Class are defendants herein, the officers and directors of the Company, at all relevant times, members of their immediate families and their legal

[7] *See* Chris Rees, "AVEO: Anatomy of a trade gone wrong," *TheStreet.com,* August 13, 2013.

representatives, heirs, successors or assigns and any entity in which defendants have or had a controlling interest.

173. The members of the Class are so numerous that joinder of all members is impracticable. Throughout the Class Period, AVEO securities were actively traded on the NASDAQ. While the exact number of Class members is unknown to Plaintiffs at this time and can be ascertained only through appropriate discovery, Plaintiffs believe that there are several hundred, if not thousands, of members in the proposed Class. According to the Annual Report that AVEO filed with the SEC on Form 10-K on March 11, 2013, AVEO had eighty-eight (88) record holders, which refers generally to the number of brokers that register shares on behalf of their clients, together with any shareholders that had specifically arranged for direct registration of shares. According to the 10-K, AVEO and its executives "believe that the number of beneficial owners of our common stock [as of February 2013] was substantially greater." Record owners and beneficial owners who may be members of the Class may be identified from records maintained by AVEO or its transfer agent and notice directed through brokers as is customarily made in securities class actions.

174. Plaintiffs' claims are typical of the claims of the members of the Class as all members of the Class are similarly affected by defendants' wrongful conduct in violation of federal law and the same misrepresentations and omissions complained of herein.

175. Plaintiffs will fairly and adequately protect the interests of the members of the Class and has retained counsel competent and experienced in class and securities litigation. Plaintiffs have no interests antagonistic to or in conflict with those of the Class.

176. Common questions of law and fact exist as to all members of the Class and predominate over any questions solely affecting individual members of the Class. Among the questions of law and fact common to the Class are:

- whether the federal securities laws were violated by Defendants' acts as alleged herein;
- whether Defendants misrepresented their regulatory communications with the FDA during the Class Period as alleged herein;
- whether Defendants concealed from investors adverse information communicated to them by the FDA regarding the FDA's concerns regarding higher risk of death for tivozanib patients in the TIVO-1 trial, and if so, whether the omitted information was material;
- whether Defendants concealed from investors adverse information communicated to them by the FDA regarding the potential impact of the higher risk of death on the approvability of tivozanib, and if so, whether the omitted information was material;
- whether Defendants concealed from investors adverse information communicated to them by the FDA regarding the FDA's request for an additional, well-controlled clinical trial in a population comparable to the United States, and if so, whether the omitted information was material;
- whether Defendants acted knowingly or recklessly in issuing false and misleading statements identified herein;
- whether the price of AVEO's common stockwas artificially inflated during the Class Period because of the Defendants' conduct complained of herein; and
- whether the members of the Class have sustained damages and, if so, what is the proper measure of damages.

177. A class action is superior to all other available methods for the fair and efficient adjudication of this controversy since joinder of all members is impracticable. Furthermore, as the damages suffered by individual Class members may be relatively small, the expense and burden of individual litigation make it impossible for members of the Class to individually redress the wrongs done to them. There will be no difficulty in the management of this action as a class action.

178. Plaintiffs will rely, in part, upon the presumption of reliance established by the fraud-on-the-market doctrine in that:

- defendants made public misrepresentations or failed to disclose material facts during the Class Period, which misrepresentations were conveyed to investors and distorted the trading price of AVEO shares during the Class Period;

- the omissions and misrepresentations were material;

- AVEO securities are traded in efficient markets;

- the Company's shares were liquid and traded with moderate to heavy volume during the Class Period;

- the Company traded on the NASDAQ, and was covered by multiple analysts;

- the misrepresentations and omissions alleged are of the type that would tend to induce a reasonable investor to misjudge the value of the Company's securities as is demonstrated by the sharp revaluation during each of the three partial disclosures alleged herein; and

- Plaintiffs and members of the Class purchased and/or sold AVEO securities between the time the defendants failed to disclose or misrepresented material facts and the time the true facts were disclosed, without knowledge of the omitted or misrepresented facts.

179. Based upon the foregoing, Plaintiffs and the members of the Class are entitled to a presumption of reliance upon the integrity of the market.

180. Plaintiffs may also rely, in part, on the presumption of reliance available for omissions under *Affiliated Ute Citizens v. United States*, 406 U.S. 128 (1972), in that the material misrepresentations alleged herein are primarily material omissions and not affirmative misrepresentations of fact.

COUNT I

(Against All Defendants For Violations of Section 10(b) And Rule 10b-5 Promulgated Thereunder)

181. Plaintiffs repeat and reallege each and every allegation contained above as if fully set forth herein.

182. This Count is asserted against all defendants and is based upon Section 10(b) of the Exchange Act, 15 U.S.C. § 78j(b), and Rule 10b-5 promulgated thereunder by the SEC.

183. During the Class Period, Defendants knowingly or recklessly misrepresented material facts and omitted to state material facts necessary in order to make the statements made, in light of the circumstances under which they were made, not misleading. Specifically, among the other misrepresentations identified in detail in the paragraphs above, Defendants: (a) misrepresented their regulatory communications with the FDA; (b) omitted material adverse information regarding study misconduct and design flaws in the TIVO-1 trial which confounded results as to both overall survival and progression-free survival, rendering the trial uninterpretable, invalid, and without any evidentiary value; (c) omitted material adverse information regarding concerns expressed to them by the FDA regarding a higher risk of death in tivozanib, and the effect of that higher risk of death upon approvability; and (d) omitted material adverse information regarding the FDA's request, communicated to them, that AVEO conduct an additional clinical trial.

184. Pursuant to this course of conduct, each of the Individual Defendants made the material misrepresentations attributed to him and participated directly or indirectly in the dissemination of the Company's misrepresentations in quarterly and annual reports, SEC filings, press releases and investor conferences.

185. As specified above, each Defendant either attended or was personally briefed on the May 11, 2012 pre-NDA meeting, Each Defendant also had access to: (a) meeting minutes from the May 2012 meeting; (b) May 12, 2012 and May 30, 2012 internal PowerPoint presentations describing the FDA's positions taken during the May 11, 2012 meeting, and the impact of those positions on AVEO's business prospects; (c) a July 2012 meeting request sent by AVEO to the FDA committing to conduct a second trial and proposing a protocol therefor; (d) an August 29, 2012 response from the FDA rejecting as deficient Defendants' proposed TIVO-2

protocol; (e) an August 31, 2012 letter from AVEO to the FDA cancelling the scheduled meeting; (f) a communication on or about that same day from Astellas warning Defendants that their action imperiled the tivozanib NDA; (g) a day-74 letter stating that the FDA remained significantly concerned about overall survival; (h) a March 8, 2013 meeting request submitting a revised proposed protocol for the second trial, and requesting that it be conducted post-approval; (i) a March 13, 2013 letter from the FDA rejecting the revised protocol, and rejecting the request to conduct the second study on a post-approval basis. Each also participated in an emergency Executive Committee meeting on May 11 or 12, 2012 to discuss the problems caused by the FDA's request for a second clinical trial, and each either participated in or was aware of a board meeting shortly thereafter budgeting $83 million for a second clinical trial, which was expected to take three years to complete.

186. Even if Defendants did not have an absolute duty to disclose the true facts alleged herein as a result of the importance of those facts to AVEO's business and prospects, each of the Defendants assumed the duty to speak wholly and truthfully to investors regarding the topics on which he spoke, including AVEO's regulatory communications, NDA and clinical trials. For the reasons specified above, Defendants understood the critical importance of the omitted information, and at least recklessly ignored the likelihood that the omissions would materially alter the total mix of information available to investors.

187. As a result of the dissemination of the aforementioned false and misleading reports, releases and public statements, the market price of AVEO securities was artificially inflated throughout the Class Period. Without benefit of the true facts misrepresented and omitted by Defendants, Plaintiffs and the other members of the Class purchased AVEO securities at

artificially inflated prices and relied upon the price of the securities, the integrity of the market for the securities and/or upon statements disseminated by defendants, and were damaged thereby.

188. Had Plaintiffs and the other members of the Class known the truth, they would not have purchased said securities or would not have purchased them at the inflated prices that were paid. At the time of the purchases by Plaintiffs and the Class, the true value of AVEO securities was substantially lower than the prices paid by Plaintiffs and the other members of the Class. The market price of AVEO securities declined sharply upon public disclosure of the facts alleged herein to the injury of Plaintiffs and Class members.

189. By reason of the conduct alleged herein, each of the Defendants knowingly or recklessly violated Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder.

190. As a direct and proximate result of Defendants' wrongful conduct, Plaintiff and the other members of the Class suffered damages in connection with their respective purchases and sales of the Company's securities during the Class Period, upon the disclosure of the truth about the Company's regulatory communications with the FDA and the design defects and scientific misconduct in their pivotal clinical trial for tivozanib, TIVO-1.

COUNT II

(Violations of Section 20(a) of the Exchange Act Against Defendant Ha-Ngoc)

191. Plaintiffs repeat and reallege each and every allegation contained in the foregoing paragraphs as if fully set forth herein.

192. During the Class Period, Defendant Ha-Ngoc controlled the operation and management of AVEO, and directed and oversaw AVEO's business and regulatory affairs and investor communications. Because of his position as AVEO's President, CEO and Director, and

for the reasons alleged herein, Defendant Ha-Ngoc knew the material adverse non-public information omitted from investors alleged above.

193. Defendant Ha-Ngoc, as a result of his role as President, CEO and Director of AVEO, had the ability to and did exercise control over AVEO and its public representations to investors and analysts. He had the obligation to disseminate only truthful information with respect to AVEO's operations and the development and regulatory progress of its key drug, tivozanib, and to correct promptly any public statements issued by AVEO which had become materially false or misleading. Defendant Ha-Ngoc, was a "controlling person" of AVEO within the meaning of Section 20(a) of the Exchange Act. In this capacity, he participated in AVEO's unlawful conduct which artificially inflated the market price of AVEO securities.

194. By reason of the above conduct, Defendant Ha-Ngoc is additionally liable pursuant to Section 20(a) of the Exchange Act for the violations committed by AVEO.

195. Defendant Ha-Ngoc, by virtue of the fact that Defendants Slichenmyer and Johnston reported to him and were subordinate to him in the corporate structure of AVEO, also had the opportunity and power to control the public statements of Defendants Slichenmyer and Johnston, and was a "controlling person" of Defendants Slichenmyer and Johnston within the meaning of Section 20(a) of the Exchange Act. In this capacity, he participated in the unlawful conduct of Defendants Slichenmyer and Johnston.

196. By reason of the above conduct, Defendant Ha-Ngoc is also liable pursuant to Section 20(a) of the Exchange Act for the violations committed by Defendants Slichenmyer and Johnston.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs demand judgment against defendants as follows:

A. Determining that the instant action may be maintained as a class action under Rule 23 of the Federal Rules of Civil Procedure, and certifying Plaintiffs as the Class representatives;

B. Requiring Defendants to pay damages sustained by Plaintiffs and the Class by reason of the acts and transactions alleged herein;

C. Awarding Plaintiffs and the other members of the Class prejudgment and post-judgment interest, as well as their reasonable attorneys' fees, expert fees and other costs; and

D. Awarding such other and further relief as this Court may deem just and proper.

DEMAND FOR TRIAL BY JURY

Plaintiffs hereby demand a trial by jury.

Dated: February 2, 2017

By their attorneys,

/s/ Adam M. Stewart

Edward F. Haber (BBO #215620)
Adam M. Stewart (BBO #661090)
SHAPIRO HABER & URMY LLP
Seaport East
Two Seaport Lane
Boston, MA 02210
Tel. (617) 439-3939
ehaber@shulaw.com
astewart@shulaw.com

POMERANTZ LLP
Patrick V. Dahlstrom
Joshua B. Silverman
Louis C. Ludwig
10 South LaSalle Street, Suite 3505
Chicago, IL 60603
Telephone: 312-377-1181
Facsimile: 312-377-1184

POMERANTZ LLP
Marc I. Gross
Jeremy A. Lieberman
600 Third Avenue, 20th Floor
New York, NY 10016
Tel. (212) 661-1100
Fax (212) 661-8665

Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that this document, filed through the ECF system, will be sent electronically to the registered participants as identified on the Notice of Electronic Filing ("NEF") on this February 2, 2017.

/s/ Adam M. Stewart
Adam M. Stewart